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The contribution of health-related quality of life and utility values to decision-making in dermatology

PhD Thesis

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List of Abbreviations

15D – 15-dimension instrument
ABQOL – Autoimmune Bullous Disease Quality of Life questionnaire
ABSIS – Autoimmune Bullous Skin Disorder Intensity Score
ADLs – Activities of Daily Livings
AI – Anxiety Index
ASQ – Anxiety Scale Questionnaire
ATT – Attitude to Appearance scale
AQoL-8D – Assessment of Quality of Life-8D
BMI – body mass index
BP – bodily pain dimension of SF-36
CADTH – Canadian Agency for Drugs and Technologies in Health
CDQ – Clinical Depression Questionnaire
COMDQ – Chronic Oral Mucosal Diseases Questionnaire
COOP – Dartmouth Primary care Cooperative Information Project
DLQI – Dermatology Life Quality Index
DSQL – Dermatology-specific Quality of Life
DQOLS – Dermatology Quality of Life Scales
Dsg – desmoglein
GH – general health dimension of SF-36
GHQ – General Health Questionnaire
HRQoL – health-related quality of life
HTA – heath technology assessment
HUI – Health Utilities Index
IgA – Immunoglobulin A
IMPACT – Impact of Skin Disease Scale
KMPI – Koo-Menter Psoriasis Instrument
LE – life expectancy
MADRS – Montgomery-Åsberg Depression Rating Scale
MAU – multi-attribute utility
MCID – minimal clinically important difference
MH – mental health dimension of SF-36
NHP – Nottingham Health Profile
NICE – National Institute for Health and Care Excellence
PASI – Psoriasis Area and Severity Index
PDAI – Pemphigus Disease Area Index
PDI – Psoriasis Disability Index
PF – physical functioning dimension of SF-36
PFo – pemphigus foliaceus
PGA – Physician's Global Assessment
PQOL – Psoriasis quality-of-life questionnaire
PsA – psoriatic arthritis
PUVA – psoralen and ultraviolet A light
PV – pemphigus vulgaris
QALY – quality-adjusted life year
QWB – Quality of Well-being Index
RE – role-emotional dimension of SF-36
SF – social functioning dimension of SF-36
SF-6D – Short form 6 dimensions
SF-36 – Medical Outcomes Study 36-Item Short Form
SG – standard gamble
SIP – Sickness Impact Profile
SPI – Simplified Psoriasis Index
SSc – systemic sclerosis
SSQ – Social Support Questionnaire
TABQOL – Treatment of Autoimmune Bullous Disease Quality of Life questionnaire
TTO – time trade-off
VAS – visual analogue scale
VT – vitality dimension of SF-36
WHODAS-II – World Health Organization Disability Assessment Schedule 2
WHOQOL – World Health Organization Quality of Life

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1 Introduction

Over the past few decades, the importance of health-related quality of life (HRQoL) has become increasingly recognised in measuring the impact of chronic diseases in a number of fields of medicine, including dermatology. This interest is reflected in the growing number of studies published investigating the effect of various illnesses and health interventions on HRQoL. Currently the term 'HRQoL' yields over 27,000 hits in PubMed[1].

Chronic skin diseases, such as psoriasis, eczema, vitiligo and pemphigus, have a profound impact on patients' HRQoL, adversely affecting everyday activities, work, relationships and leisure time, among others. Additionally, in modern societies, where greater importance is attached to appearance and beauty, patients with visible lesions on the skin often experience stigmatisation, which may increase the risk of mental illness and social isolation [1, 2]. The assessment of HRQoL is widely used to explore the burden experienced by patients with chronic skin diseases in everyday clinical settings, as well as in various dermatological researches, including observational and interventional studies. In dermatology, a growing number of randomised controlled trials (RCTs) apply HRQoL measures as secondary or tertiary endpoints to evaluate treatment efficacy [3, 4]. This can be particularly informative when HRQoL does not correlate strongly with disease severity, for instance in psoriasis, hand eczema or alopecias [5-7]. Thus, HRQoL and severity scores complement each other in understanding individual patients' health status as a whole and contribute to reaching optimal clinical decisions for each patient.

As HRQoL outcomes reflect patients' perspectives about the burden of their skin disease, they thus engage patients as active partners in decisions related to their medical care. During the management of dermatological issues, several clinical decisions seem to be supported by information on HRQoL: diagnostic criteria, treatment choices, treatment monitoring or hospitalisation decisions. Besides its role in medical decision-making, assessing improvements in HRQoL with a therapy provides useful information for payers and policymakers about the benefits of certain treatments. Life years saved as the result of a treatment, and improvements achieved in HRQoL, are considered as two major

[1] 'Health-related quality of life' - text-word search in PubMed on 24th January, 2016

outcomes. The availability of highly effective but very costly treatments in dermatology, such as biological drugs, is rapidly expanding, thereby exerting growing pressure on health budgets. Health interventions resulting in more benefits in terms of HRQoL (and life years saved) for the same or lower costs are deemed to be cost-effective in comparison to alternative treatments [8]. Moreover, choosing the right cost-effective options improves efficiency in the allocation of finite resources in healthcare and helps to maximise value for money for patients and society.

There exists a wide range of literature with a number of outcome measures which address HRQoL issues in various chronic skin diseases. Nonetheless, very few studies have been undertaken in this area in Hungary specifically, and in a broader sense Central and Eastern Europe. For reimbursement decisions, though, national guidelines on health technology assessments (HTAs) recommend collecting HRQoL values derived from national-level surveys [9].

This thesis therefore seeks to investigate HRQoL in chronic skin diseases in Hungary, with a special focus on issues influencing clinical and financial decision-making in healthcare. The first chapter provides a description of the two dermatological conditions covered, namely psoriasis and pemphigus, a brief overview of the key terms and definitions used and an introduction to the background of the assessment of HRQoL in dermatology.

In the following chapters, new empirical findings are presented from three independent investigations, carried out by our research group in Hungary between 2012 and 2015 [10-16]. First, a cross-sectional survey on health status and HRQoL among Hungarian moderate-to-severe psoriasis patients was conducted (‘Psoriasis study’). The second investigation (‘Pemphigus study’) is covered in two parts: a systematic literature review and a meta-analysis of HRQoL studies in pemphigus, as well as a valuation of utilities for pemphigus health states in the general population. The third research (‘DLQI study’) explores the relationship between a dermatology-specific HRQoL measure, namely the Dermatology Life Quality Index (DLQI), and health utilities within the framework of an Internet experiment carried out with members of the general public.

1.1 Description of the diseases covered in the thesis

The disease-specific studies in this thesis focus on two chronic dermatological conditions, psoriasis and pemphigus.

1.1.1 Psoriasis

Aetiology and epidemiology

Psoriasis is a chronic, inflammatory, immune-mediated condition with a complex aetiology of genetic and environmental risk factors [17, 18]. The prevalence of psoriasis varies across geographical regions, age groups and ethnicities [19]. In Europe, among individuals of all ages, the prevalence ranges between 0.73% and 2.9%, and incidence stands at about 120-140 out of 100,000 people [19]. No data are available from Hungary on the epidemiology of psoriasis.

Comorbidities

Psoriasis is often associated with multiple comorbidities, including psoriatic arthritis, inflammatory bowel diseases, diabetes, metabolic syndrome, obesity, dyslipidaemia, cardiovascular disease and psychological or psychiatric disorders [20, 21]. It is estimated that around 10-40% of all patients develop psoriatic arthritis [22]. Severe psoriasis patients may have an increased risk of mortality due to various causes, amongst which cardiovascular disease is the most common [23].

Clinical characteristics

Five clinical types of psoriasis are known, among which chronic plaque psoriasis (i.e. psoriasis vulgaris) is the most prevalent. It is typically characterised by raised, well-demarcated, erythematous plaques with adherent silvery scales. Primary predilection sites include elbows, knees and the scalp. It may remain localised or become generalised over time. Guttate (or eruptive) psoriasis is manifested in scaly teardrop-shaped spots. Inverse (or intertriginous) psoriasis usually develops in skin folds, such as armpits, the groin or inframammary folds. Pustular psoriasis is an uncommon variant, which can present as localised to the palms and soles (palmoplantar pustulosis) or become generalised.

Furthermore, erythrodermic psoriasis is a rare but severe form of the disease that can either develop acutely or follow a chronic course [24-27].

Diagnosis

The diagnosis of psoriasis vulgaris is based primarily on clinical appearance and predilection sites. The removal of psoriatic scales may cause multiple fine bleeding points, known as Auspitz's sign. Rarely, a histological examination of a skin biopsy is needed to confirm the clinical diagnosis [28].

Outcome measures

The severity of psoriasis is classified into two main categories (mild and moderate-to-severe) based on three outcome measures: body surface area (BSA), the Psoriasis Area and Severity Index (PASI) and the Dermatology Life Quality Index (DLQI) [29].

The BSA percentage indicates how much of the body's surface is affected by psoriasis. Traditionally, the patient's palm is considered equal to 1% of BSA [30].

PASI is a quantitative rating scale for psoriasis based on the severity of the lesions, judged on the coverage area and plaque appearance. To calculate PASI scores, the body is divided into four distinct regions based on the estimated area of the skin affected (head=0.1, upper extremities=0.2, trunk=0.3 and lower extremities=0.4). Each area is rated by itself from 0 to 6, where 0=0%, 1=1-9%, 2=10-29%, 3=30-49%, 4=50-69%, 5=70-89% and 6=90-100% involvement. The severity of plaques is graded by the presence of three clinical signs: erythema, induration and desquamation (measured on a scale of 0-4, with 4 being the worst). The total PASI score ranges from 0 to 72, with higher scores referring to greater disease severity [31-33].

The DLQI is a dermatology-specific HRQoL questionnaire validated for measuring HRQoL in psoriasis [34]. The ten-item questionnaire's scale ranges between 0 and 30, where higher scores indicate the worst disability experienced by patients. See the DLQI in detail in *Chapter 1.3.2.4.*

Based on these three outcome measures, mild plaque psoriasis is defined as (BSA ≤ 10 or PASI ≤ 10) and DLQI ≤ 10, whereas (BSA > 10 or PASI > 10) and DLQI > 10 suggests a moderate-to-severe disease (*'rule of tens'*) [29, 35].

Treatment

The recommendations of the European S3-Guidelines on the treatment of psoriasis are based on disease severity [28]. Topical agents, including calcipotriol, corticosteroids, dithranol and calcineurin inhibitors such as tacrolimus, are used as first-line treatments of mild disease. In moderate-to-severe psoriasis patients, the following traditional systemic treatments are suggested: cyclosporine, methotrexate and psoralen combined with ultraviolet-A light (PUVA). Biological systemic treatment (adalimumab, etanercept, infliximab or ustekinumab) is recommended to a patient if conventional systemic agents have been inadequate in response, or if they are contraindicated or not tolerated [28].

1.1.2 Pemphigus

Epidemiology

Pemphigus is a rare autoimmune disease blistering disease that may affect the skin and mucosa. It has an annual incidence of 0.1 and 7 per million [36]. The mean age of onset is usually between the ages of 50 and 60, but it can develop at any age. Other autoimmune conditions, such as myasthenia gravis and thyroid diseases, often develop in pemphigus patients [37, 38].

Clinical forms

Clinically, the two most common forms of pemphigus are pemphigus vulgaris (PV) and pemphigus foliaceus (PFo), which differ in their target antigens, the location of lesions within the epidermis as well as their symptoms. In Europe and the US, the most common clinical type is PV, whereas in Africa pemphigus foliaceus is more frequent [39]. In PV, autoantibodies are directed predominantly against desmoglein (Dsg)-3 together with Dsg1 of desmosomes (macula adherens), whereas solely Dsg-1 antibodies are produced in PFo. The regional expression pattern of the two antigens targeted by the autoantibodies is reflected in the location of skin lesions in different pemphigus forms. In PV, mucous

membranes, especially those of the oral cavity, are very frequently affected, because Dsg-3 is expressed strongly in mucosae and weakly in the epidermis. In contrast, Dsg-1 is expressed mainly in the upper levels of the epidermis, just below the stratum corneum, but weakly in mucosae. Oral lesions are thereby not common in PFo. In PV, on the contrary, bullae develop just above the basal-cell layer, as Dsg-3 is present primarily in the deeper layer of the epidermis while absent in the superficial layer [39, 40].

Clinical characteristics

Typically, PV begins with multiple, painful, non-healing ulcerations in the oral cavity. Other mucosae, such as the nasal cavity, pharynx, larynx, oesophagus, genital mucosae and the rectum, may as well be involved. The first skin symptoms may follow mucosae involvement weeks or even months later. The scalp and the torso are very commonly affected. Blisters are usually flaccid, and applying lateral pressure on the border of an intact blister results in the separation of the epidermis (positive Nikolsky's sign). Skin lesions in the superficial form, PFo, usually manifest in multiple, pruritic and crusted erosions on the upper torso, face and the scalp. The crusts can be removed easily, leaving superficial erosions [39-41].

Outcome measures

A number of scoring systems have been developed and validated to quantify disease severity in pemphigus based on the global assessment of the lesions [42].

The Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) is a complex pemphigus scoring system that considers both the extent and the severity of cutaneous as well as oral pemphigus lesions. First, skin involvement is assessed by weighting the BSA (%) by the quality of the lesions. Weighting factors are as follows: erosive, exudative lesions or a positive Nikolsky's sign 1.5, dry lesions 1.0 and re-epithelised lesions 0.5. Secondly, oral involvement is rated based on the presence of lesions on 11 different sites of the mouth. The severity of oral symptoms is scored by the pain or bleeding caused by certain foods (always=1, sometimes=0.5, never=0). The total score ranges from 0 to 150, where a higher score indicates greater severity [43].

In the Pemphigus Disease Area Index (PDAI), the lesions are categorised in relation to the skin (12 body sites), the scalp (one body site) and mucous membranes (12 areas). The skin and the scalp components consist of activity and damage scores. Activity scores are obtained based on the number of erosions, blisters or new erythema, whereas damage scores are given based on the presence of post-inflammatory hyperpigmentation or erythema from resolving lesions. The total score varies between 0 and 263, where higher scores indicate the worst disease severity [42, 44].

The Ikeda-index has four domains (affected area percentage, Nikolsky's sign, daily number of new blisters and oral lesions in percentage), with each being scored from 0 to 3. The sum total score of the four domains ranges from 0 (best) to 12 (worst) [45].

Diagnosis

The diagnosis of pemphigus is based on four independent criteria: clinical presentation, histopathology, direct immunofluorescence microscopy of perilesional skin and the serological detection of serum autoantibodies against epithelial cell surface antigens (Dsg-1 and Dsg-3) by indirect immunofluorescence microscopy and/or enzyme-linked immunosorbent assays [46].

Treatments

If left untreated, the blisters and/or erosions spread, which can be potentially life-threatening. With proper treatment, however, pemphigus usually heals without scarring. According to the European S2 Guideline for the diagnosis and treatment of pemphigus (2015), the current therapeutic algorithm includes systemic corticosteroids as a first-line treatment, followed by azathioprine, mycophenolat mofetil or mycophenolic acid as a second-line treatment. In refractory pemphigus patients, or when glucocorticoids and immunosuppressants are contraindicated, rituximab (anti-CD20 monoclonal antibody) intravenous immunoglobulins, immunoadsorption, cyclophosphamide, dapsone or methotrexate are recommended [46].

1.2 Key terms and definitions of the thesis

1.2.1 Health-related quality of life

The World Health Organization (WHO) defines quality of life as an *[''individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.'']* [47]. Quality of life covers several domains of life, including physical health, psychological health, personal beliefs, social relationships and the environment.

In medicine, the term '*health-related quality of life*' (HRQoL) is preferred; however, it extends far beyond physical health alone. HRQoL comprises three core domains, namely physical, psychological and social, which interact with each other and are influenced by an individual's experiences, beliefs, perceptions and expectations. Each incorporates many components; for example, the physical domain includes symptoms, disability and the ability to function, whereas the social domain refers to areas of work, daily role and personal relations. It is not hard to imagine, therefore, that the possible number of health states is almost infinite; two patients with the same diagnosis and severity scores may differ significantly in their HRQoL [48-50].

1.2.2 The concept of utility

Utility is a cardinal measure of the desirability or preference that individuals exhibit for a given condition [51, 52]. The term refers to the *von Neumann-Morgenstern utility theory* for decisions under uncertainty [53], and it assumes that people strive to maximise a weighted sum of utilities, where the weights are probabilities and choices between gambles or lotteries containing goods and services. The following axioms undermine the theory, where A, B and C are lotteries [54]:

- *Transitivity*: if lottery A is preferred or indifferent to lottery B, and B is preferred or indifferent to lottery C, then A is preferred or indifferent to C
- *Continuity:* there is an indifference curve such that all points to its northeast are preferred to all points to its southwest

- *Completeness*: either lottery A is preferred to B, and lottery B is preferred to lottery C, in which case there is some combination of A and C that will be preferred to B
- *von Neumann-Morgenstern independence*: adding a third lottery to two lotteries, whose ranking has already been determined, will not affect that ranking [54].

Utilities represent a widely used approach to the measurement of HRQoL. Utility values, or in other words HRQoL weights, can be assessed for any health state and reflect the HRQoL accordingly [52]. Generally, utilities are expressed in an interval scale anchored to 0 and 1, where 0 indicates death and 1 indicates perfect health. In many studies, however, health states can take a negative utility between zero and minus infinity, if judged as being worse than being dead [55].

As HRQoL outcomes are used to help healthcare decision making, utilities are particularly appropriate measures of HRQoL, given their foundation in decision theory [52].

1.2.3 Quality-adjusted life year

The time spent in health states is weighted by the utility for health states to calculate the unit of *quality-adjusted life year* (QALY). Thus, QALYs combine the effects of a health intervention on mortality and morbidity into a single index. One QALY is equal to one life year in perfect health. It is a standard health outcome that permits the comparison between different health interventions for different diseases. The QALY is needed for the cost-utility analysis, which is a special form of cost-effectiveness analysis [56, 57]. The primary outcome of cost-utility analysis is the incremental cost-effectiveness ratio, which indicates the additional cost per QALY gained. When comparing alternative treatments, a health intervention that generates a lower cost per QALY ratio is preferred to that of a higher cost per QALY ratio [8].

1.3 Background to the assessment of HRQoL in dermatology

1.3.1 Burden of chronic skin diseases

The impact of dermatological diseases on patients' HRQoL is very heterogeneous in terms of the affected domains and the magnitude of impairment. Some minor dermatological conditions, such as verruca vulgaris or onychomycosis, slightly influence HRQoL, whereas life-long chronic skin diseases, including psoriasis, may profoundly alter patients' lives as a whole. Certain skin diseases reduce HRQoL, albeit only in individual domains; for instance, hand dermatitis leads to decreased HRQoL mainly in the domains of work and household activities [58]. In contrast, patients with rosacea experience the most problems in the mental health and social relationship areas [59]. In the most severe skin diseases, however, all dimensions can be adversely affected: daily routine, work, leisure time, social relationships, sex life, sports and sleeping [60].

A large selection of physical symptoms, such as pain, pruritus and fatigue, can be associated with skin diseases. These vary from minor irritation of the skin to severely painful lesions. Pruritus, a common and very unpleasant symptom present in many dermatological diseases, may lead to severe deterioration in HRQoL [61, 62]. Furthermore, many skin diseases are systemic conditions that impose an additional physical burden on patients; for instance, systemic sclerosis or psoriatic arthritis is often associated with restricted mobility.

A special aspect of HRQoL in dermatology is that skin lesions, especially when manifested on the face, neck, hands or nails, are visible to others. The feeling of stigmatisation is very commonly reported among dermatological patients as a result of embarrassment, decreased self-esteem, psychological distress and the avoidance of social activities [63, 64]. It is therefore not surprising that anxiety, depression, suicidal ideation and many other mental health problems frequently occur in these patients [2, 65].

A recently advocated new concept, the *Cumulative Life Course Impairment* (CLCI) approach, suggests that the negative impact of chronic skin diseases on HRQoL cumulates throughout a patient's lifetime [66]. The CLCI stems from a complex interaction between the burden of stigmatisation, physical and psychological impairment,

coping strategies and several external factors, such as social support [66-69]. As a result, in the long term, major life-changing decisions related to education, career choice, having children, getting married and travelling could be influenced by chronic skin disease [70, 71].

The consequences of the limitations in HRQoL include the secondary negative impact on a patient's family, work productivity and financial status. Skin disease can interfere with the family members and partners of patients in many ways, of which the burden of extra housework, psychological pressure (e.g. worrying about the patient), limitations to holiday plans, leisure activities and sexual relationships are very commonly mentioned concerns [72, 73].

Patients regularly miss working hours or whole workdays due to visits to physicians, treatments or the illness itself (*absenteeism*). The skin disease, however, may have a negative influence on work performance, too (*presenteeism*). In hand eczema or psoriasis, the physical burden of work or the regular irritation of the skin often force patients to quit their jobs. Patients with moderate-to-severe skin diseases are also more likely to be unemployed [74-77].

The costs of skin disease, including co-payments (e.g. drugs, physician visits), as well as the cost of transportation to physicians and caregivers places a great financial burden on patients [78-80]. High costs can be attributed to cosmetic products, careful choices of clothing and other devices (e.g. wigs for alopecia patients). Furthermore, the household income of patients with severe skin diseases may be significantly reduced [81, 82].

1.3.2 Methods employed to assess HRQoL and utilities in dermatology

This section provides a brief overview of the most commonly used HRQoL tools in dermatology. Special emphasis is given to those involved in the original researches of this thesis. The domains and scoring for all HRQoL instruments related to this thesis are detailed in *Appendix 12.1*.

In general, HRQoL measures aim at detecting changes in HRQoL and discriminate between patients who have a better and those who have a worse HRQoL.

There are no best or worst instruments – the choice of the instrument usually depends upon the purpose of the study, the condition studied, the characteristics of the study population (e.g. age, health status and language) and the method of data collection (e.g. clinical trial, outpatient visit, postal or Internet survey) [83].

There are two basic approaches to the assessment of HRQoL: *preference-based* and *non-preference based* methodologies (*Figure 1)*. The difference between these two large groups of methodologies is the ability to provide utility values. Only preference-based instruments enable one to calculate utility values, and thus they can be used in economic evaluations. Non-preference-based measures, nevertheless, are widely used in clinical trials to explore changes to HRQoL across several dimensions. A variety of non-preference based instruments exist, and these either cover all aspects of patients' lives that an illness can affect (*generic instruments*) or are specific to a group of diseases (*dermatology-specific instruments*) or to individual diseases (*disease-specific instruments*) [84].

Preference-based measures are generally classified into direct and indirect methods of utility assessment. In *direct methods*, patients or members of the general public value hypothetical or experienced health states. In *indirect methods*, patients complete a multidimensional HRQoL questionnaire, and then a tariff obtained from the general population is used to transform the patients' answers into utility weights [85-87]. Of course, patients know their disease best; yet, people who experience a certain disorder tend to rate it as less severe than people who do not have it [88]. Some reasons identified to contribute to this discrepancy include: i) patients and the general public may understand the health state vignettes differently; ii) general population members may not consider adaptation to health states; iii) a response shift in how people rate health states as a result of getting ill or changing expectations and iv) focusing illusion, whereby people forget to consider obvious aspects of unfamiliar health states [87]. Therefore, utility values are somewhat influenced by the populations who elicit them in the first place.

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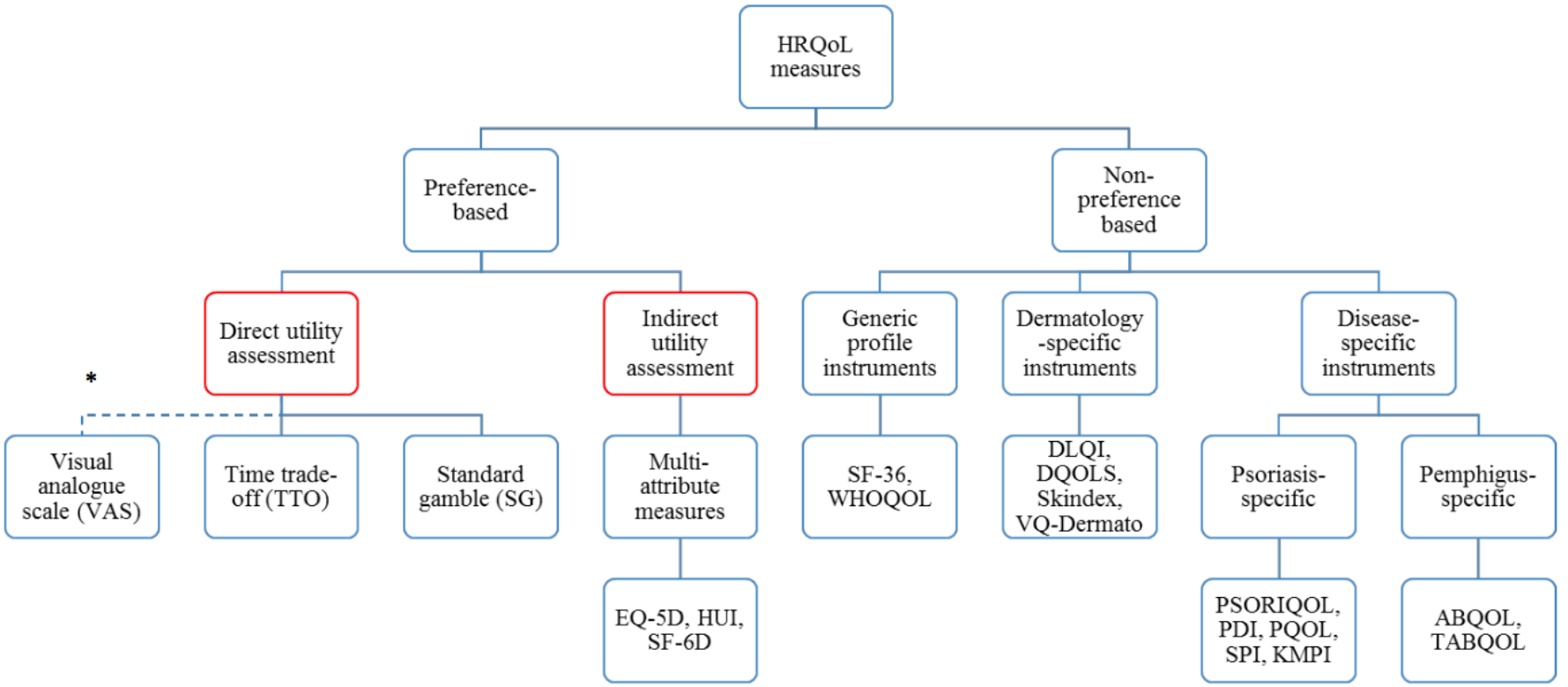

Figure 1 Measurement of HRQoL in dermatology

* VAS, TTO and SG are so-called 'direct preference elicitation methods', although VAS is not preference-based.
ABQOL = Autoimmune Bullous Disease Quality of Life questionnaire; DLQI = Dermatology Life Quality Index; DQOLS = Dermatology Quality of Life Scales; DSQL = Dermatology-specific Quality of Life; HUI = Health Utilities Index; KMPI = Koo-Menter Psoriasis Instrument; PDI = Psoriasis Disability Index; PQOL = Psoriasis quality-of-life questionnaire; SF-6D = Short form 6 dimensions; SF-36 = Medical Outcomes Study 36-Item Short Form; SG = standard gamble; SPI = Simplified Psoriasis Index; TABQOL = Treatment of Autoimmune Bullous Disease Quality of Life questionnaire; TTO = time trade-off; VAS = visual analogue scale

In countries with publicly-funded healthcare systems, the allocation of healthcare resources should, or would be expected to, take into account social preferences. Based on this notion, in many jurisdictions, HTA agencies such as the US Public Health Service Panel on Cost Effectiveness in Health and Medicine [89], the National Institute for Health and Care Excellence (NICE) [90] in the UK and the Canadian Agency for Drugs and Technologies in Health (CADTH) [91] recommend that utility values should be based on the preferences of the adult general population, rather than on patient preferences. Similarly, in Hungary, HTA guidelines provided by the Ministry of Human Resources promote the use of such utility weights in economic analyses of health technologies [9].

1.3.2.1 Direct utility assessment

There have been three major direct techniques developed to elicit utility values: the *visual analogue scale* (or rating scale), *standard gamble* (SG) and *time trade-off* (TTO).

Visual analogue scale

The visual analogue scale (VAS) is a graphical form of rating scales. A typical VAS consists of a straight, vertical or horizontal line with two clearly defined endpoints. These endpoints are usually marked with labels corresponding to 'best imaginable health state' (or 'perfect health') and 'worst imaginable health state' (or 'being dead'). Numbers may also be used as anchors; for example, 100 or 10 or 1 often represent the most preferred outcome, whereas 0 is the least preferred option. Subjects are asked to mark their rating of a health state on the scale, which in most cases lies between the two anchors [51, 52].

Simplicity and the easiness of administration make VAS a very attractive instrument. However, it is often considered inferior to TTO and SG, because these both require respondents to express their preferences about health states and to make decisions that have an opportunity cost in the form of sacrificed life years in the TTO task or the certainty of survival in SG [92, 93].

Standard gamble

The standard gamble (SG) method is based directly on the *von Neumann-Morgenstern* utility theory. In SG exercises, subjects are offered two options. They can choose between the certainty of remaining in an impaired health state for a defined time duration or they

can take a risk of either regaining perfect health (probability p) or facing immediate death (probability 1-p). The probability of immediate death is varied until the subject becomes indifferent in relation to the two alternatives. At this point the utility for the impaired health state is equal to the probability of regaining perfect health (p) [51, 52, 94, 95].

In the field of dermatology, the SG methodology has been applied successfully in atopic dermatitis, psoriasis, scleroderma and melanoma [96-100].

Time trade-off

The time trade-off method (TTO) is the most frequently applied approach for the direct assessment of utilities [101]. The methodology was developed specifically by Torrance [95] for use in healthcare settings. In TTO, subjects are asked to choose between two alternatives: living a longer period of time in a worse health state or a shorter period in a better health state (perfect health or the absence of a given disease). The amount of time offered in perfect health varies until the subject becomes indifferent in relation to the two options. Utility values for the impaired health state are calculated by dividing the number of years in perfect health by the number of years in impaired health [51, 52, 94, 95].

No uniform methodology currently exists to value health states by TTO; studies can differ considerably regarding many aspects, such as mode of administration, time frame, visual aids used, iteration procedure, definition of the best and worst health states and the subjects who elicit utilities (e.g. patients or general population) [102, 103].

Increasing numbers of studies apply the TTO methodology for dermatological research [104, 105]. In 2004, Chen et al. provided a preliminary repository of utilities in 17 dermatological conditions by conducting TTO interviews at three dermatologic clinics in the US [106]. Besides, a few studies of individual diseases were undertaken in psoriasis, atopic dermatitis, scleroderma, acne, port-wine stain and melasma [98, 100, 107-109].

1.3.2.2 Indirect utility assessment: multi-attributable utility measures

Multi-attribute utility (MAU) instruments are generic or disease-specific HRQoL questionnaires which consist of a descriptive or a self-classification system, including a

series of HRQoL items, together with a scoring algorithm. Responses can be either aggregated into dimension scores or subscale scores to establish the responder's health profile, or they can be transformed into a single utility score by the scoring algorithm. These algorithms, often so-called 'tariffs' or 'weights', are usually obtained from a general population sample by a direct elicitation method (e.g. VAS or TTO) [110-112].

The main advantages of MAU instruments are that they are flexible and easy to administer; however, the utility scores generated may depend largely on the algorithm used. There are six generic MAU measures that dominate the literature: the Quality of Well-being Index (QWB), 15 dimension instrument (15D), EuroQol-5-dimensions (EQ-5D), the three versions of the Health Utilities Index (HUI 1-3), Short form 6D (SF-6D) and Assessment of Quality of Life (AQoL-8D). Of these, the EQ-5D is by far the most commonly employed tool [110-112].

EQ-5D

EQ-5D is a five-item MAU instrument that assesses health status across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [113, 114]. Each domain has three response levels (no problems, some problems, severe problems), and accordingly 3^5=243 combinations of health states are possible. A series of country-specific scoring algorithms is available to calculate EQ-5D index scores (i.e. utility), but no Hungarian tariff has been developed, to date. It is accompanied by a visual analogue scale (EQ VAS) that is a 20 cm-long, vertical visual analogue scale with endpoints of '0' (worst possible health state) and '100' (best possible health state) recording patients' self-rating of their overall health, which also enables determining utilities.

The EQ-5D has been translated into over 170 languages, it is cognitively simple and takes only a few minutes to complete [115]. Over the past two decades, population health surveys using the EQ-5D have reported population reference values from some 20 countries [116]. In Hungary, two large sets of population norms are available, and the data collection periods for these were in 2001 and 2010 [117, 118].

In some countries, such as the UK and the US, the EQ-5D has become a favoured measure of utilities for economic analyses [89, 90]. Similarly, current HTA guidelines in

Hungary advocate the use of indirect measures, particularly the EQ-5D, to derive utility values [9].

A recent systematic literature review concluded that the EQ-5D has good validity and responsiveness in patients with skin disease, especially in plaque psoriasis [119]. To date, it has been applied in many skin conditions other than psoriasis, such as acne, atopic dermatitis, hand eczema, herpes zoster, hidradenitis suppurativa and venous leg ulcers [119, 120]. However, only two studies can be found in the literature utilising the EQ-5D in Hungarian patients with dermatological conditions, and these concentrate on psoriatic arthritis and scleroderma [121, 122].

1.3.2.3 Generic profile instruments (non-preference-based)

Generic measures were designed to give a general overview of HRQoL. The main advantage of these instruments is that they allow comparisons among different populations regardless of the underlying condition. Commonly used non-preference-based generic profiles are the Sickness Impact Profile (SIP), Medical Outcomes Study 36-Item Short Form (SF-36), the Nottingham Health Profile (NHP) and the Dartmouth Primary care Cooperative Information Project (COOP) [48, 83, 123].

SF-36

The Short form 36 (SF-36) is the most commonly used and validated generic profile measure of health status in dermatological research [124]. It includes 36 items on a Likert-scale format to assess the following eight dimensions of health: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). Scores on each domain range from 0 to 100, with higher scores indicating a better health state. The PF, RP, BP and GH subscales are summarised into a Physical Component Summary (PCS) score, and VT, SF, RE and MH to a Mental Component Summary (MCS) score [125, 126].

General population norms for SF-36 are available from many countries that show the typical levels of HRQoL in these eight domains. In light of comparisons between patients and population reference values, physicians as well as payers can understand which domains of HRQoL are impaired – and to what extent – for a given condition. To

date, SF-36 has been employed in almost every chronic dermatological condition, including psoriasis, atopic dermatitis, contact dermatitis, chronic urticaria, pemphigus, acne, rosacea, alopecias and vitiligo [58, 59, 124, 127, 128].

1.3.2.4 Dermatology-specific HRQoL measures

Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is the most commonly used HRQoL instrument in the field [3, 34, 129]. The questionnaire contains ten items, each of which is scored from 0 to 3, where 0 - not at all/not relevant, 1 - a little, 2 - a lot, and 3 - very much. The results of each item are summed into a total score ranging from 0 (best health state) to 30 (worst health state). A banding system helps the interpretation of scores developed by Hongbo et al. [130]. A DLQI score of 0-1 has been interpreted as 'no effect on patient's life', 2-5 as 'small effect', 6-10 as 'moderate effect', 11-20 as 'very large effect' and 21-30 as 'extremely large effect' [130].

In the past two decades, it has developed into a valid and reliable tool for HRQoL assessment in a variety of dermatological conditions [129]. Its advantages include brevity, easiness to administer and multilingual availability. So far, the DLQI has been used in over 30 different dermatological conditions [3]. The most common applications are psoriasis, atopic dermatitis, vitiligo, urticaria, contact dermatitis and acne [3, 129].

Its appropriateness as an outcome measure, however, has been disputed by many. A few studies have argued that factor-analysis and Rasch-analysis question the unidimensional construct of the DLQI, thereby suggesting that certain items of the measure are not independent [131-135]. It has been also addressed that it exhibits differential item functioning, in that the results are biased by the age, gender, disease, and nationality of patients [132, 133, 136].

Skindex

Skindex-29 is a validated dermatology-specific HRQoL measure comprising three subscales: symptoms (seven items), emotions (10 items) and functioning (12 items). Item responses are transformed to a scale from 0 (no effect) to 100 (maximum effect), and subscale scores are calculated as the average of the patients' responses to the items in a

given domain [137]. Two brief versions of Skindex-29 exist: Skindex-17 and Skindex-16 [138, 139].

Skindex instruments have been applied in a series of chronic dermatological conditions, both in observational and interventional studies: acne, actinic keratosis, atopic dermatitis, fungal diseases, hand dermatitis, hyperhidrosis, psoriasis, rosacea, scalp dermatitis and vitiligo [124, 140].

1.3.3 Use of HRQoL measures in dermatology

The assessment of HRQoL in dermatology is driven by multiple purposes, including clinical, research, economic and financial.

Clinical

In many chronic skin diseases HRQoL does not always correlate with disease severity [5-7]. Thus, disease severity measures alone are insufficient to capture the entire burden of skin diseases, and HRQoL and severity scores are suggested to be measured together, in order to provide a clear picture of an individual patient's health status. Population norms are available for many instruments that allow one to compare a patient's HRQoL to the reference values of the general population. This comparison outlines which domains of HRQoL are particularly impaired in a patient, and to what extent [141, 142].

Currently, information on the HRQoL of dermatologic patients is embedded in clinical decision-making in many ways: diagnostic criteria, treatment choices, treatment monitoring and decisions about admission to hospital. However, the contribution of HRQoL data to medical decisions varies according to diagnosis, disease severity and the type of treatment. HRQoL outcomes are the most explicitly present in the management of moderate-to-severe psoriasis, where diagnostic criteria include a dermatology-specific HRQoL tool, namely the DLQI. In psoriasis, (BSA>10 or PASI>10) and DLQI >10 can be considered a moderate-to-severe disease, and it is recommended to be treated with phototherapy or systemic treatments including biologicals (see in details: *Chapter 1.1.1*) [22, 23]. The European-S3 Guidelines on the systemic treatment of psoriasis vulgaris lists HRQoL among the outcomes required to be measured before and during systemic therapy [28]. More specifically, DLQI, Skindex-29 or -17 are among the instruments suggested

to be administered. In judging treatment response, a DLQI < 5 or, alternatively, a DLQI improvement of at least five points is often considered a minimum efficiency goal of systemic therapy [28].

Similarly, European guidelines on the treatment of atopic dermatitis and acne promote the assessment of HRQoL [143, 144]. Nevertheless, no specific tool or severity score is proposed. In these conditions, therefore, the role of HRQoL in clinical decisions is more uncertain compared to that in psoriasis. This is well-exemplified in the European-S3 guidelines for the treatment of acne, which states the following about the necessity of measuring HRQoL: *[''The impact of acne on quality of life can be measured using general health measures, dermatology-specific measures or acne-specific measures.] ... [Quality of life measures can influence the choice of therapy. In patients with a severe impact on their quality of life, a more aggressive therapy may be justified.'']* [143].

Research

HRQoL measures are used in epidemiologic as well as in clinical research. A large number of different dermatology- and disease-specific measures are available for dermatological researches. These may differ in how they define HRQoL, their domains, the amount and quality of psychometric testing and validation [145]. There have been a number of sharp debates as to which HRQoL instruments should be used in dermatology [124, 131-134, 136, 146, 147].

A review by Both et al. provides a detailed comparison of generic health profiles and dermatology-specific questionnaires in terms of psychometric properties, scoring, administrative burden, respondent burden and cultural and language adaptations. This intends to help researchers to make an evidence-based choice of instrument that fits for the purposes and design of the study [124]. The choice of instrument transpires to be even more important, as HRQoL has become an accepted outcome measure of clinical efficacy in RCTs [3]. In psoriasis, for example, the European Medicines Agency recommends the use of DLQI as a secondary or tertiary endpoint to assess the efficacy of treatment [148]. It is also being used increasingly by many RCTs in atopic dermatitis [4]. Along with the DLQI, Skindex instruments are used in more and more RCTs across many skin conditions, including psoriasis, atopic dermatitis and acne [140]. What is more promising,

though, is that growing numbers of psoriasis RCTs apply preference-based HRQoL measures, such as the EQ-5D [149-151]. In psoriasis, this trend apparently coincides with the development of biological drugs. In other chronic dermatological diseases, however, there is a paucity in the administration preference-based instruments in RCTs [4, 152].

Economic

HRQoL data assessed with preference-based instruments can be used for the calculation of QALYs in cost-utility analyses of health interventions (see details in *Chapter 1.2.3*). In non-life-threatening chronic skin diseases, the improvement in HRQoL following treatment is responsible for the majority of the QALY gain. Thus, the accurate measurement of HRQoL with respect to the choice of instrument, study design and patient population is crucial, as it has a direct impact on the outcomes of economic evaluation.

Over the past decade, the number of cost-utility analyses published on dermatological treatments has been rising. Studies include tacrolimus [153], pimecrolimus [154, 155] and prebiotics for atopic dermatitis [156] and oral alitretinoin (a derivative of vitamin A) for severe chronic hand eczema [157]. Nevertheless, treatments for psoriasis, more specifically biological drugs, represent by far the most studied area. A recently published systematic review of cost-effectiveness analyses in psoriasis identified 15 cost-utility examples in the literature [158]. The treatments studied were as follows: calcipotriol, calcipotriol and bethamethasone, methotrexate, ultraviolet B phototherapy and biological drugs [158].

Financial

In several countries, dermatology-specific HRQoL measures, such as DLQI and Skindex, are used in national reimbursement guidelines to determine whether a patient should be considered for treatment. Examples include the financing of biological therapy for moderate-to-severe psoriasis and oral alitretinoin for severe chronic hand eczema [159].

In the UK, Sweden, Denmark and six Central and Eastern European countries, including Hungary (*Table 1*), reimbursement criteria on financing biological therapy for moderate-to-severe psoriasis patients are based on DLQI scores alongside PASI and BSA [148, 160, 161]. Severity scores eligible for reimbursement vary across jurisdictions. In

the UK, for example, patients who accomplish PASI ≥10 and DLQI>10, in Hungary PASI>15 and DLQI>10 or in Croatia PASI>15 and/or BSA>15 and/or DLQI>15 are entitled to be treated with biologicals. In the Netherlands, Skindex-29 scores are used instead of DLQI in reimbursement criteria, whereby patients with PASI > 10 or (PASI > 8 and Skindex-29 > 35) qualify for biological therapy [161].

Not only the initiation of biological therapy, but also eligibility for maintenance therapy is decided based on DLQI scores. In most Central and Eastern European countries, maintenance therapy is allowed for patients who reach a response of ≥50% reduction in PASI, and in addition a ≥5-point improvement in DLQI (*Table 1*) [148].

Table 1 DLQI in biological reimbursement eligibility criteria for psoriasis in Central and Eastern European countries

	Clinical severity criteria for being eligible to start covered biological therapy	**Criteria of eligibility for maintenance therapy (at week 12)**
Bulgaria	PASI >20 or BSA>20	PASI improvement ≥75%; or PASI improvement ≥50% and DLQI improvement ≥ 5 points
Croatia	PASI >15 and /or BSA>15 and/or DLQI>15	PASI improvement ≥50% and DLQI improvement ≥ 5 points
Czech Republic	PASI>10 and DLQI>10	PASI improvement ≥50%
Hungary	PASI>15 and DLQI>10	PASI improvement ≥50% and DLQI improvement ≥ 5 points
Poland	PASI>18, DLQI>10, and BSA>10	PASI improvement ≥50% and DLQI improvement ≥ 5 points
Romania	PASI ≥ 10 and DLQI≥10	PASI improvement ≥50% and DLQI improvement ≥ 5 points

BSA = body surface area; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index
Source: Rencz et al. 2015 [148]

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2 Objectives

2.1 Psoriasis study

The objectives of this cross-sectional study were:

1. To evaluate the health status and HRQoL of adult moderate-to-severe psoriasis patients in Hungary, to explore differences in HRQoL among subgroups of patients and to compare EQ-5D results to general population norms in Hungary;
2. The assessment of patients' subjective life expectancy (LE) and expected HRQoL for six months ahead and for future ages of 60, 70, 80 and 90, respectively.

2.2 Pemphigus study

Systematic review and meta-analysis of HRQoL studies

Our aims were:

1. To conduct a systematic review of the existing literature on the impact of pemphigus on HRQoL;
2. To perform a meta-analysis on the outcomes of the most frequently used HRQoL instruments;
3. To identify the possible determinants of HRQoL in pemphigus.

Valuation of pemphigus health states by the general population

This study aimed:

1. To elicit utility values for hypothetical pemphigus vulgaris and pemphigus foliaceus health states, using two direct methods, VAS and TTO, in a general population sample.
2. To compare the utilities assigned to different pemphigus health states.

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2.3 DLQI study

The objectives of the study were:

1. The estimation of utilities for different health states described by the 10 items of the DLQI by the TTO method;
2. To compare utility values elicited for health states with identical and different DLQI total scores.

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3 Methods

3.1 Psoriasis study methods

3.1.1 Study design

A cross-sectional questionnaire survey of consecutive adult psoriasis patients from two Hungarian university clinics was carried out between September 2012 and May 2013. The study protocol was approved by the Scientific and Research Ethics Committee of the Medical Research Council of Hungary (ETT TUKEB), reference No. 35183/2012-EKU. We planned to enrol approximately 100 patients from each clinic. Patients of 18 years of age or over, who were diagnosed with moderate-to-severe psoriasis (PASI > 10 or DLQI > 10, or being treated by systemic or biological therapy) at least 12 months before the time of the survey, were included in the study. Data were collected by dermatologists during outpatient visits at Semmelweis University, Department of Dermatology, Venereology and Dermatooncology (Budapest) and at the University of Debrecen, Departments of Dermatology and Dermatological Allergology. Written informed consent was obtained from all patients [162, 163].

3.1.2 Outcome measures and assessment

Patients and their physicians were asked to complete a self-designed questionnaire. The patients' questionnaire consisted of demographic data, the family history of psoriasis, disease duration, affected body sites and HRQoL measures. HRQoL was captured by the validated Hungarian versions of EQ-5D-3L descriptive system (hereinafter EQ-5D) and visual analogue scale (EQ VAS) and a dermatology-specific measure, namely the DLQI. The description and scoring of EQ-5D and DLQI are outlined in *Chapter 1.3.2*. We applied the UK tariff to calculate EQ-5D index scores (range -0.594 to 1). Further questions concerned visit(s) to a general practitioner in the last month, to a dermatologist in the last three months and hospitalisation(s) in the last 12 months (all due to psoriasis). The necessity of home help in the last month and work impairment due to psoriasis were also recorded. In the second part of the questionnaire, dermatologists were asked to provide data on the clinical type of psoriasis and treatments in the last 12 months

based on medical records. PASI was used to assess the severity of psoriasis. PASI is described in detail in *Chapter 1.1.1*.

3.1.3 Measuring patients' expectations

To elicit patients' future expectations, we employed the descriptive system of the EQ-5D instrument, as was done previously in two large surveys on the general population in the Netherlands and Hungary, as well as in a recent study with Hungarian rheumatoid arthritis patients [164-166]. As the EQ-5D is set up to measure current health, we modified the time frame. Patients were asked to indicate the HRQoL they expected to have at six months ahead and at the age of 60, 70, 80, and 90 years, respectively (*Table* **2**). The rationale behind the choice of six months was that this duration was assumed long enough to result in a considerable improvement in HRQoL following successful therapy, but short enough to be easily conceived.

Table 2 Modified EQ-5D-3L to evaluate expectations regarding future HRQoL

I think at age 60 I will have… (Please mark your response)				
a.	no	some	major	problems with walking about.
b.	no	some	major	problems with washing or dressing.
c.	no	some	major	problems with performing usual activities.
d.	no	some	severe	pain or discomfort.
e.	no	some	severe	anxiety or depression.

*Ages 70, 80 and 90 were asked in the same construct

We measured a point estimate of subjective life expectancy (LE) for each patient by asking them, *"To what age do you expect yourself to live?"* Patients were instructed not to answer questions about future ages they had already reached, and the responses of those who answered in spite of the request were excluded. The responses of patients who indicated an age higher than 100 years were truncated to 100.

3.1.4 Statistical analysis

First, descriptive statistics of sociodemographic and clinical characteristics of the sample are presented. As the distribution of data was skewed, non-parametric statistics (Wilcoxon signed-rank test, Mann-Whitney U test and Kruskal-Wallis test) were used. Spearman's correlations were applied to analyse the relationship between continuous variables, such as actual and expected EQ-5D index score, EQ VAS, DLQI, PASI, subjective LE and HRQoL expectations. A Spearman's rank coefficient (r_s) of 0-0.19 is defined as very weak, 0.20-0.39 as weak, 0.40-0.59 as moderate, 0.60-0.79 as strong and 0.80-1 as a very strong correlation [167].

EQ-5D results, in terms of both dimension percentages and index scores, were compared with the Hungarian general population norm published by Szende and Németh in 2003 [118]. Patients who did not indicate their subjective LE, their actual EQ-5D or their expected EQ-5D for six months were excluded from the analysis of expectations. For all respondents, we calculated the difference between their gender- and age-specific statistical life expectancy (actual LE) based on their subjective LE and data retrieved from the Hungarian Central Statistical Office (KSH) [168]. We computed the difference in HRQoL expectations between patients expecting to be alive at a given age ('survivors') and those not expecting to live ('non survivors'). Finally, expectations on HRQoL for older ages were compared to the actual health statuses of the age-matched psoriasis patients within the sample. All the applied statistics were two-sided with a significance level of $p<0.05$. Statistics were performed with IBM SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

3.2 Pemphigus study methods

3.2.1 Systematic review of HRQoL studies in patients with pemphigus

3.2.1.1 Search strategy

A systematic search was conducted using the following databases from their inception to 6 October, 2014: Ovid Medline, EMBASE, Web of Science, CINAHL, PsycINFO, and the Cochrane Library. The search strategy *(Appendix 12.2)* designed for this study included a combination of terms related to pemphigus, general HRQoL terms, names of generic and dermatology-specific instruments and HRQoL assessment methods based on the recommendations of Paisley et al. [169]. The search excluded publications of the following types: comments, editorials, letters or conference papers. No language limits were applied. In addition, the references of all included studies were searched for eligible studies. Review articles were excluded; however, their reference lists were also examined for relevant studies.

3.2.1.2 Selection of the studies

Titles and abstracts of the identified records were screened by two independent researchers (Fanni Rencz and Valentin Brodszky). Any disagreement was resolved through discussion until consensus was reached. Only records meeting the following inclusion criteria were selected for a full-text review:

- The study population included adult pemphigus patients;
- The study reported HRQoL in pemphigus patients assessed by any instrument;
- Publication type: original article not a review or a conference abstract or proceeding.

During the full-text review, all papers meeting any of the following criteria were excluded:

- No HRQoL outcome reported;
- Only aggregate HRQoL values were available for a group of skin diseases;
- Full-text article not available.

3.2.1.3 Data extraction

The following data were extracted from all included studies: patient characteristics (sample size, pemphigus type, mean age, disease duration, sex ratio, current therapy, and geographic location), applied HRQoL instruments, HRQoL scores and determinants of general or dermatology-specific HRQoL analysed statistically in the studies. We considered significant the relationship between determinants and HRQoL, if a significant unidirectional relationship with HRQoL was justified in ≥2 studies.

3.2.2 Meta-analysis

For meta-analysis, the number of patients, mean HRQoL scores and standard deviations (SD) were extracted from each study, and 95% confidence intervals were calculated. Where SD was not reported, we replaced it by the average SD of the other studies.

Meta-analysis was carried out on total scores or individual domains of HRQoL instruments on which results were reported in at least three separate studies including patients of similar characteristics. Data were pooled by using the inverse-variance weighted method. Heterogeneity across studies (i.e. variability in HRQoL as a consequence of clinical and methodological diversity) was analysed using the Cochran's Q and the I^2 statistics [170]. Where significant heterogeneity was detected across studies (Cochran's $Q<0.01$ or $I^2>50\%$), a random-effects meta-analysis (DerSimonian and Laird method) was applied [171]; otherwise, a fixed-effects model was employed. In random-effects meta-analysis it is assumed that each study is derived from a different population of patients; therefore, the true effect size is not identical in all studies, though they do have enough in common to conduct a meta-analysis. All statistics were two-sided, and a $p<0.05$ was considered statistically significant, except where otherwise stated. Microsoft Excel 2013 was used for the statistical analyses.

3.2.3 Valuation of pemphigus health states by the general population

3.2.3.1 Study overview

A convenience sample of adults aged ≥18 years and able to understand the Hungarian language were recruited at the campus of Corvinus University of Budapest between December 2014 and May 2015. Data were collected using a paper-based questionnaire in group interviews. Participation in the study was voluntary, and respondents did not receive any compensation. Ethical approval was obtained from the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (reference No. 275./2014).

The groups consisted of up to 20 participants, and the average length of interview was 17 minutes. The interviews were led by two researchers (Fanni Rencz and Valentin Brodszky), both of whom had previous experience in leading TTO interviews. Subjects who decided to participate in the study were asked to fill in a self-completed questionnaire. However, during the interview process, respondents had the opportunity to ask the interviewer any question about the task.

In the first section of the questionnaire, respondents were asked about their sociodemographic characteristics and whether they had any prior knowledge about pemphigus (e.g. had they ever heard about it, know someone with pemphigus, ever seen pemphigus patient(s) or been diagnosed with pemphigus?). Then, in the main part of the questionnaire, participants evaluated three hypothetical pemphigus health states by VAS and TTO. To help them understand the TTO task, we offered a warm-up question that involved a binocular blindness health state.

3.2.3.2 Health state descriptions

The results of our systematic review (*Chapter 4.2.1*), the items of a recently developed blistering skin disease-specific questionnaire, the Autoimmune Bullous Disease Quality of Life (ABQOL) [172] and consultations with two dermatologists were used to create three pemphigus health states: uncontrolled PV, uncontrolled PFo and controlled pemphigus. In the controlled state we did not distinguish between PV and PFo. The health

state vignettes were pilot-tested in four pemphigus patients at the Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, in order to determine the clarity of descriptions and the TTO task.

The health state vignettes provided a brief description of living with pemphigus, including experienced physical symptoms, possible food avoidance and issues about daily activities and social life from the second-person perspective (*Table 3*). The participants were asked to read the vignettes carefully and imagine being in the health state described. The order of the three health states within the questionnaire was as follows: uncontrolled PV, controlled pemphigus and uncontrolled PFo.

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Table 3 Pemphigus health state descriptions

	Uncontrolled pemphigus vulgaris	Uncontrolled pemphigus foliaceus	Controlled pemphigus
Skin symptoms	Blisters and erosions develop on approximately 25-30% (=25-30 palms) of your skin. The blisters are around 1-3 cm in diameter, very itchy and painful when appear. Bursting blisters may bleed and leave raw, red areas on your skin. After healing, your skin becomes pigmented.	Erosions and scaling wounds develop on approximately 10-15% (=10-15 palms) of your skin. The erosions are around 1-3 cm in diameter, moderate-itchy and painful. Wounds typically heal slowly, and after healing your skin becomes pigmented.	A few blisters or erosions can be seen on your skin and lips. The blisters are around 0.5-2 cm in diameter, a little itchy and rarely painful.
Food avoidance	There are erosions in your mouth and tongue, so you try to avoid hard (e.g. apple, fried steak, bread), spicy or acidic foods/drinks (e.g. tomato, orange, alcohol), which can cause sore and/or gingival bleeding.	There are no erosions in your mouth, so you can eat and drink what you want.	There are no erosions in your mouth, so you can eat and drink what you want.
Bathing/clothing	Showering/bathing and washing your hair can be very painful. You typically avoid any tight clothes and often wear gauze between your skin and clothes to prevent rubbing and bursting of the blisters.	Showering/bathing and washing your hair can be very painful. You typically avoid any tight clothes and often wear gauze between your skin and clothes to prevent rubbing of the blisters.	Showering/bathing and washing your hair can be a little bothersome. You can wear any clothes you want.
Work	Your skin condition leads to decreased productivity at the workplace and many sick days.	Your skin condition leads to decreased productivity at the workplace and many sick days.	Your skin condition does not affect your productivity at the workplace, you rarely miss work due to physician visits or treatments.
Social life	You feel embarrassed and anxious in the company of others due to your visible skin lesions.	You feel embarrassed and anxious in the company of others due to your visible skin lesions.	You only sometimes feel embarrassed and anxious in the company of others due to your visible skin lesions.

3.2.3.3 Utility assessment

We followed the checklist for utility assessment proposed by Stalmeier et al. [55]. In this study, two direct methods, VAS and TTO, were employed to value health states. The methodological background, as well as the use of these two measures in earlier dermatological research, is described in *Chapter 1.3.2.1*.

Visual analogue scale

Participants were asked to place each hypothetical health state on a horizontal 100-mm VAS ranging from 0 (worst possible health state) to 100 (best possible health state), which were then transformed to utilities (range 0-1).

Time trade-off

A new approach, the composite TTO, described by Janssen et al. [173] and applied in this study, is a combination of a conventional TTO for health states better than dead and a lead time TTO for states valued as worse than dead. This method proved feasibility and face-validity, and compared to the conventional TTO it led to a more consistent elicitation of negative values [173]. We decided to use a 10-year time frame, as this was used for the valuation of the EQ-5D health states in the Measurement and Valuation of Health study [174]. For worse than dead health states, a lead-time-to-disease time ratio of 1:1 was applied.

All valuations started with a conventional TTO as described by Gudex et al. [175]. The participants were instructed to choose between 10 years in a pemphigus health state versus a shorter life in perfect health. In order to conform to the self-completion methodology of our study, the iteration procedure was amended compared with that of Janssen et al. [173]. The top-down titration procedure was used by starting with 10 years in perfect health and descending to 0 years (10, 9.5, 9, 8, 7, etc.) (*Figure 2*) [175].

In the lead time TTO, respondents who preferred 0 years in perfect health (i.e. chose immediate death) over 10 years in a pemphigus health state were given 10 more years spent in perfect health before the 10 years to live in pemphigus (a total of 20 years). The alternative option offered ranged between 10 years and 0 years in perfect health (*Figure 3*).

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PEMPHIGUS		CANNOT DECIDE	PERFECT HEALTH	
10 YEARS			X	10 YEARS
10 YEARS			X	9.5 YEARS
10 YEARS			X	9 YEARS
10 YEARS		X		8 YEARS
10 YEARS	X			7 YEARS
10 YEARS	X			6 YEARS
10 YEARS	X			5 YEARS
10 YEARS	X			4 YEARS
10 YEARS	X			3 YEARS
10 YEARS	X			2 YEARS
10 YEARS	X			1 YEAR
10 YEARS	X			0 YEARS =IMMEDIATE DEATH

Figure 2 Example for a conventional TTO self-completion sheet for health states better than dead

PERFECT HEALTH	PEMPHIGUS		CANNOT DECIDE	PERFECT HEALTH	
10 YEARS	10 YEARS			X	10 YEARS
10 YEARS	10 YEARS			X	9.5 YEARS
10 YEARS	10 YEARS			X	9 YEARS
10 YEARS	10 YEARS			X	8 YEARS
10 YEARS	10 YEARS		X		7 YEARS
10 YEARS	10 YEARS	X			6 YEARS
10 YEARS	10 YEARS	X			5 YEARS
10 YEARS	10 YEARS	X			4 YEARS
10 YEARS	10 YEARS	X			3 YEARS
10 YEARS	10 YEARS	X			2 YEARS
10 YEARS	10 YEARS	X			1 YEAR
10 YEARS	10 YEARS	X			0 YEARS =IMMEDIATE DEATH

Figure 3 Example for a lead time TTO self-completion sheet for health states worse than dead

For the better than dead responses, utilities (U) were calculated by dividing the point of indifference between the two options by 10 years. For instance, if a respondent chose to live four years in perfect health over 10 years in a pemphigus health state, we get U = 8 / 10 = 0.8 (*Figure 4*). For worse than dead answers, if a participant has indicated that seven years in pemphigus is equal to 10 years in perfect health followed by 10 years

in pemphigus, the utility was estimated as U = (7-10)/10 = -0.3 (*Figure 5*). The range of TTO utilities in this study was -1 to 1, where U≤0 indicates states worse than dead.

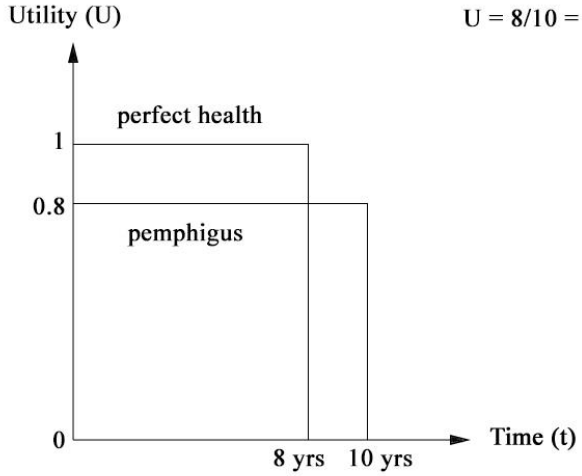

Figure 4 Calculation of utilities for health states better than dead

Source: own figure based on Torrence et al. 1986, p.23 [51]

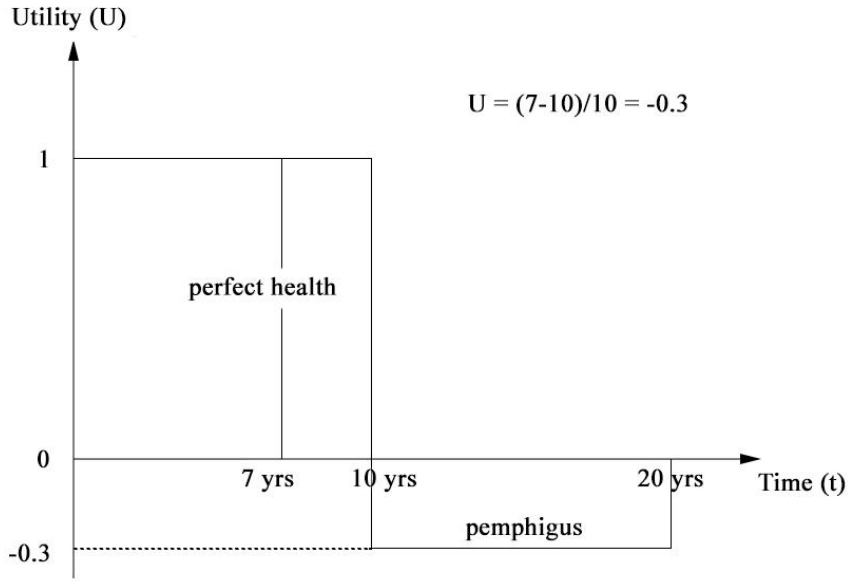

Figure 5 Calculation of utilities for health states worse than dead

Source: own figure based on Torrence et al. 1986, p.24 [51]

3.2.3.4 Statistical analysis

In a sample size calculation, we estimated that in order to detect a difference of 0.10 with an assumed SD of 0.25 between TTO utilities with a two-sided α=0.05 and 80% power, we would need 64 observations per health state [106]. This was increased by 15% in order to enable using non-parametric statistics, as suggested in the literature [176]. Our sample size target was therefore at least 74 responses for each pemphigus health state.

All non-missing TTO responses were included in the analyses. As a sensitivity analysis, we eliminated inconsistent responses and repeated all analyses.

VAS and TTO utilities, and the differences in utilities between the three health states, were compared by employing a Wilcoxon signed-rank test. The impact of gender, level of education and employment status on utilities was assessed by a Mann-Whiney U test. Spearman's rank order correlation was used to analyse the relationship between utilities and the participants' age. All statistics were two-sided, and a $p<0.05$ was taken as statistically significant. Data analysis was carried out in SPSS 22.0 (Armonk, NY: IBM Corp. 2013).

3.3 DLQI study methods

3.3.1 Design and setting

A convenience sample of university students and staff was recruited at the campus of Corvinus University of Budapest, in order to participate in a cross-sectional survey. The questionnaire was administered through the Internet in March 2015. Inclusion criteria for the study included being able to understand Hungarian and aged 18 years or over. Individuals were invited to participate regardless of having any dermatological condition at the time of the survey. No remuneration was offered for completing the survey. The experiment was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (reference No. 58./2015).

The questionnaire consisted of three sections, each of which was displayed on a separate sheet. First, demographics (gender, age, level of education and employment) and data on any dermatological condition(s) diagnosed by a physician at the time of the survey were collected. On the second page, a warm-up TTO binocular blindness exercise was introduced to familiarise the respondents with health state valuations. Finally, each respondent valued three DLQI health states. The order of health states within the questionnaire was randomised for each subject.

3.3.2 Health state descriptions

The DLQI questionnaire is presented in detail in *Chapter 1.3.2.4.* We selected seven different DLQI health states: three of 11 points (labelled as L1-L3, where L is for large impact on HRQoL), three others of six points (M1-M3 where M refers to moderate impact on HRQoL) and one of 16 points (S, for the most severe health state) (*Table 4*).

The 11-point health states were chosen, as Hongbo et al. described that a DLQI score greater than 10 indicates that the skin disease is having a very large impact on the patient's life, and this is considered to be strong supportive evidence for the need for active patient intervention [130]. The difference between health states was set at 5 points, because this exceeds the minimal clinically important difference (MCID) for general inflammatory skin diseases (4 points) [3, 177].

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Table 4 Seven DLQI health states

Health state	DLQI item scores	Total DLQI score (0-30)	Impact on quality of life*
L1	3003020003	11	very large
L2	2111111111	11	very large
L3	1200300320	11	very large
M1	3300000000	6	moderate
M2	0001110111	6	moderate
M3	2020002000	6	moderate
S	3222212101	16	very large

* Hongbo, 2005 [130]
In the names of health states, L refers to large impact on HRQoL, M refers to moderate impact on HRQoL and S is for the most severe health state.

Only one health state of 16 points was selected, because we assumed this degree of HRQoL impairment as so severe that it was unlikely to result in significantly different utilities between health states of identical total scores. Amongst the 6- and 11-point states, we intended to compile as many different health state profiles as possible in terms of:

- Affected items;
- The total number of negatively affected items;
- The severity level of impairment (i.e. the scoring of DLQI items from 0 to 3).

Similarly to the 'Pemphigus study', a second-person point of view was applied in the description of health states. The descriptions contained neither labels nor names of any specific dermatologic conditions. We made no changes to the original 10 items of the DLQI (including the bold font words) with the exception of the order of the questions. To make any differences between health states easily perceivable, we rearranged the 10 items, which were classified into two to four blocks based on the severity level of impairment (*Figure 6*). Thus, items with 'very much' impairment or 'prevented work or studying' moved to the top, followed by items affected 'a lot', 'a little' and finally 'not at all'. In the original questionnaire, eight DLQI items also had 'not relevant' options, which were scored, as they were 'not at all' answers. In this study, we did not add any 'not relevant' responses to the health state descriptions.

Affects you very much:
Your skin affects your **social** or **leisure activities** very much.
Your skin creates very much problems with your **partner** or some of your **close friends** or **relatives**.
Affects you a lot:
You are **embarrassed** or **self-conscious** a lot because of your skin.
Your skin causes a lot **sexual difficulties**.
Affects you a little:
Your skin is a little **itchy, sore, painful** or **stinging**.
Does not affect you at all:
Your skin does not interfere with you at all going **shopping** or looking after your **home** or **garden**.
Your skin does not influence at all the **clothes** you wear.
Your skin does not make it difficult at all to do **sports**.
Your skin is not a problem at all at **work** or **studying**.
Treatment of your skin, for example by making your home messy, or by taking up time, is not a problem at all.

Figure 6 DLQI health state description example: 'L3'

3.3.3 Time trade-off

The study was carried out in accordance with the checklist for utility assessment proposed by Stalmeier et al. [55]. We opted to perform the utility assessment in a general population sample because of the following reasons:

i) We intended to avoid biases on selecting a patient population with a particular diagnosis;
ii) Utilities from the general population are recommended to be used for reimbursement decisions in healthcare in many jurisdictions, including Hungary [9, 89-91];
iii) A series of outcome measures can be found in other fields of medicine, for which utilities were derived from a general population sample, e.g. Asthma Quality of Life Questionnaire, Overactive Bladder Questionnaire, Short Bowel Syndrome health-related quality of life scale, Myelofibrosis-Symptom Assessment Form, European Organisation for Research and Treatment of Cancer Quality of Life 30 Questionnaire [178-180].

The TTO task was identical to the utility assessment for better than dead health states in the 'Pemphigus study' (*Chapter 3.2.3.3*). Missing or inconsistent TTO responses were excluded from the analysis. Respondents who were unable to provide a valid answer within any TTO task were excluded from the whole study.

3.3.4 Statistical analysis

A sample size calculation was performed. We estimated that in order to detect an expected difference of 0.10 with an assumed SD of 0.25 between utilities [106], 100 valid responses would be necessary per health state to achieve a power of 80% and α=0.05 (running a two-tailed test). However, the distribution of health utilities is typically skewed because of being bounded by the limits of the scale (here: 0, 1) [181]. Thus, we increased the estimated sample size by 15% to enable using non-parametric tests [176]. We aimed to reach 115 observations per health state.

Descriptive statistics were performed to examine demographics. A Mann-Whitney U test was applied to compare utilities for different health states and the respondents' answers, with or without any dermatological condition. In a sensitivity analysis, we eliminated all responses from respondents with any dermatological condition and repeated all analyses. All statistics were two-tailed at the 0.05 significance level. Data were analysed using SPSS 22.0 (Armonk, NY: IBM Corp. 2013).

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4 Results

4.1 Psoriasis study

4.1.1 Patient characteristics

A total of 200 patients with moderate-to-severe psoriasis participated in the survey. Sociodemographic and clinical characteristics of the patients are described in *Table 5*. The mean age was 51 years (range 21-85 years), and 69% were male. Almost 80% were overweight (body mass index, BMI≥25). Two-thirds of the patients were married or cohabiting. The majority had completed secondary education (79%), and one-fifth reported to have a college or a university degree. Despite 174 (87%) patients being of working age, only 100 (50%) were employed. Overall, 21% were disabled pensioners, 19% were retired, 4% were unemployed and 2% were students. Net monthly income in 78% of the patients was equal to or less than HUF 150,000 (EUR 526)[2].

The mean disease duration was 22 years. Seventy-two (36%) patients reported a family history of psoriasis. The following clinical subtypes occurred in the sample: chronic plaque psoriasis (63%), nail psoriasis (36%), scalp psoriasis (35%), psoriatic arthritis (29%), inverse psoriasis (9%), palmoplantar psoriasis (6%), erythrodermic psoriasis (2%) and guttate psoriasis (2%) (combinations are possible).

Out of the 200 patients, 30% had been hospitalised at least once due to psoriasis in the last 12 months, and 80% had made at least one visit to a dermatologist in the last three months. Few patients (14%) used professional or informal home help. At the time of the survey, 103 (52%) received biological drug in mono- or combination therapy, 61 (31%) systemic non-biological therapy, 30 (15%) only topical treatment and six (3%) were untreated. Methotrexate (17%) and retinoids (7%) were the most commonly applied systemic non-biological therapies, whereas infliximab (19%) and adalimumab (17%) were the most frequent biological agents used. Eighteen patients (9%) were about to start their first biological drug (*Table 5*).

[2] EUR 1 = HUF 285 (year 2014)

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Table 5 Socio-demographic and clinical characteristics of the psoriasis patient population

Total (N=200)			
Mean (SD)		***Number of patients (%)***	
Age (years)	51.2 (12.9)	**Clinical subtypes****	
Psoriasis duration (years)	22.0 (11.7)	Chronic plaque psoriasis	126 (63%)
Body mass index (BMI) (kg/m^2)	29.9 (5.5)	Erythrodermic psoriasis	4 (2%)
EQ-5D index (-0.594-1)	0.69 (0.31)	Guttate psoriasis	4 (2%)
EQ VAS (0-100)	64.43 (21.34)	Inverse psoriasis	18 (9%)
DLQI (0-30)	6.29 (7.29)	Nail psoriasis	71 (36%)
PASI (0-72)	8.01 (10.01)	Scalp psoriasis	69 (35%)
Number of patients (%)		Psoriatic arthritis	57 (29%)
Gender (male)	137 (69%)	Palmoplantar psoriasis	12 (6%)
Positive family history (missing n=1)	72 (36%)	**Number of present clinical subtypes**	
Married/cohabiting (missing n=1)	131 (66%)	0 (asymptomatic at the time of the survey)	57 (29%)
Education		1	33 (16%)
Primary school	43 (22%)	2-3	83 (42%)
Secondary school	117 (59%)	≥4	27 (14%)
College/university	40 (20%)	**Health services**	
Employment (missing n=4)		Visit(s) to general practitioner (last one month) *	49 (25%)
Full-time	79 (40%)	Visit(s) to dermatologist (last three months)*	159 (80%)
Part-time	21 (11%)	Hospitalisation (last 12 months)*	59 (30%)
Unemployed	7 (4%)	Use of professional or informal home help (last one month)	27 (14%)
Disabled pensioner*	41 (21%)	**Present treatment**	
Retired	38 (19%)	*Not treated*	*6 (3%)*
Student	2 (1%)	*Topical treatments*	*30 (25%)*
Other	8 (4%)	*Systemic non-biological treatments*	*61 (32%)*
Net monthly income (HUF) (missing n=10)		Methotrexate	35 (17%)
< 75,000	78 (39%)	Cyclosporine	7 (4%)
75,001-150,000	78 (39%)	Phototherapy	5 (3%)
150,001-250,000	21 (11%)	Retinoid	14 (7%)
250,001-350,000	7 (4%)	*Biological treatment*	*103 (52%)*
> 350,000	6 (4%)	Adalimumab	33 (17%)
		Etanercept	16 (8%)
		Infliximab	38 (19%)
		Ustekinumab	16 (8%)
		First biological is indicated at the time of the survey	*18 (9%)*

* Due to psoriasis. ** Combinations may occur.

4.1.2 Health status and HRQoL in psoriasis patients

Psoriasis patients' mean EQ-5D, EQ VAS, DLQI and PASI scores were 0.69±0.31, 64.43 ±21.34, 6.29±7.29 and 8.01±10.01, respectively. Overall, 51 patients (25%) marked the best possible health state in EQ-5D (11111). Ten patients (5%) rated their health status as being worse than dead (i.e. negative EQ-5D scores). Most patients reported problems in the pain/discomfort domain of the EQ-5D descriptive system (60%), followed by mobility (47%), anxiety/depression (47%), usual activities (39%) and self-care (14%) (*Figure 7*). The highest rates of patients indicating extreme problems were noted in the pain/discomfort (9%) and anxiety/depression domains (7%).

4.1.3 Comparison of health status of patients and the general population

General health status of psoriasis patients measured by EQ-5D dimension percentages was found to be worse compared to the age-matched general population in Hungary (*Figure 7*).

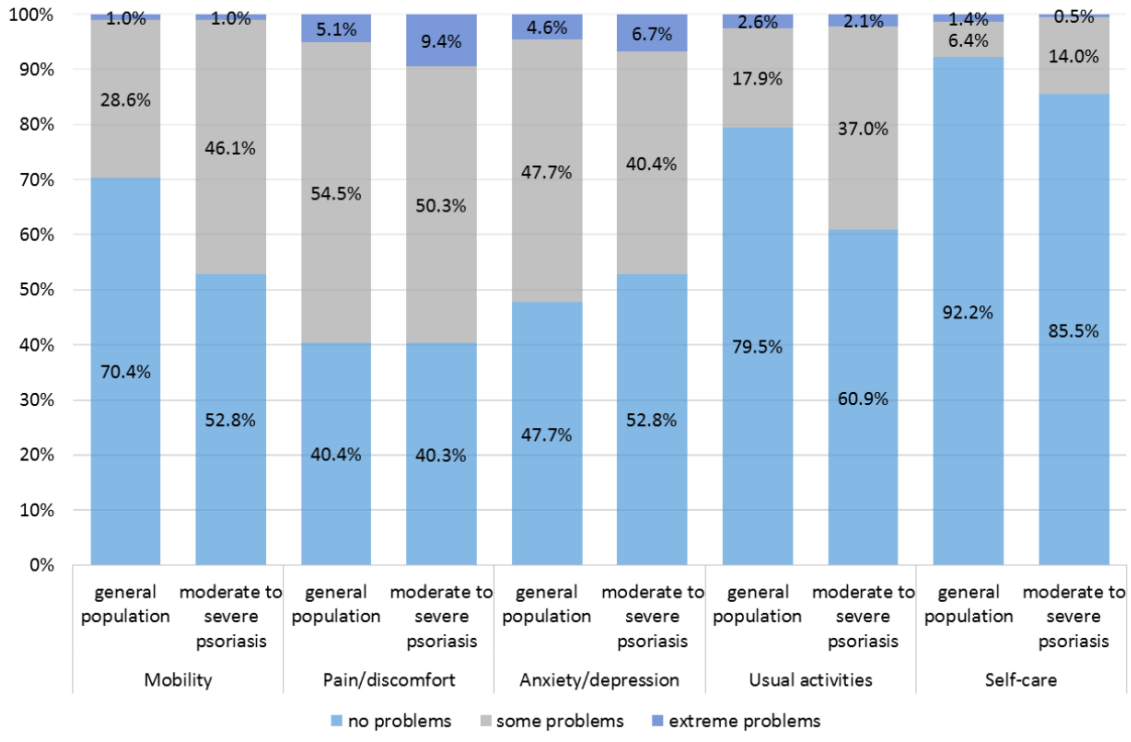

Figure 7 Comparison of EQ-5D dimensions between moderate-to-severe psoriasis patients and the general population

General population norm: Szende-Németh 2003 [118]

Similarly, we found EQ-5D index scores in patients of both females and males with psoriasis lower compared to the general population (*Figure 8*). The difference was significant for the age groups 18-24, 25-34, 45-54 and 55-64 in males, and 35-44, 45-54 and 55-64 in females ($p<0.05$).

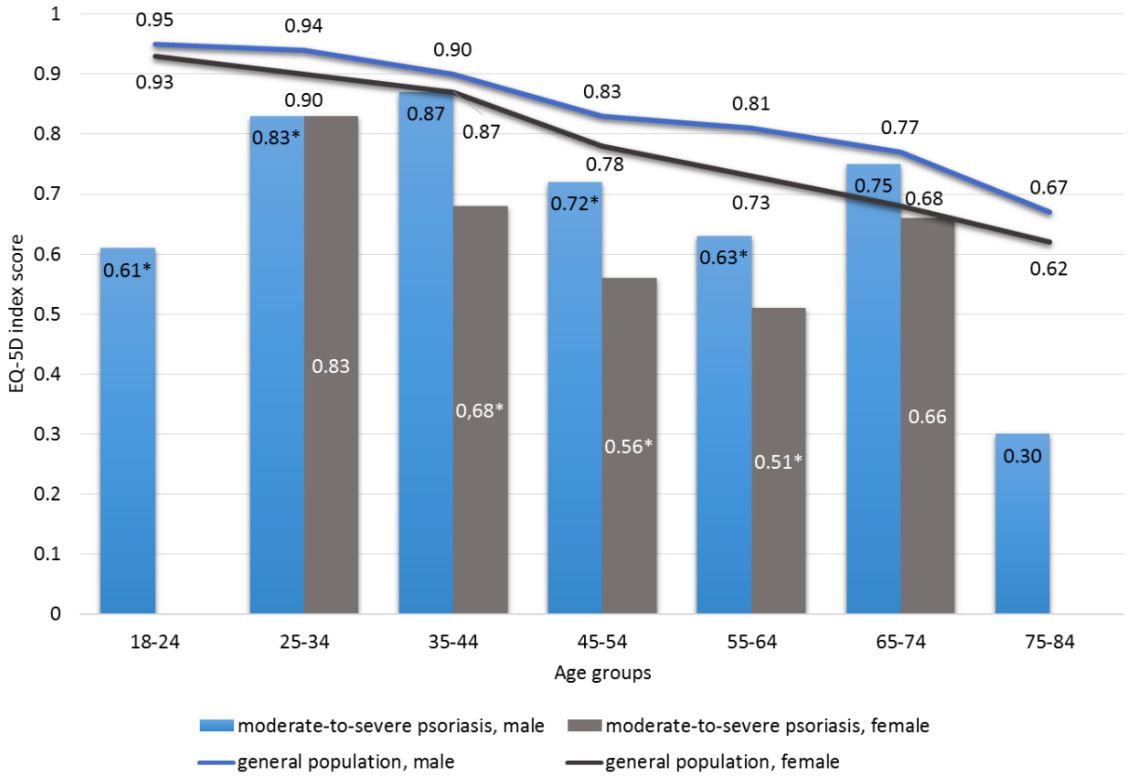

Figure 8 Comparison of mean EQ-5D index scores between moderate-to-severe psoriasis patients and the general population by age group

General population norm: Szende-Németh 2003 [118]
* significant difference ($p<0.05$)

4.1.4 HRQoL and disease severity in patient subgroups

The comparison of EQ-5D, EQ VAS, DLQI and PASI scores between patient subgroups is presented in *Table 6*. Despite the lack of significant difference in PASI scores between the two genders, female patients showed lower EQ-5D scores compared to males (0.62 vs. 0.73, $p<0.001$). No significant difference was identified between genders in EQ VAS (62.9 and 65.1, $p=0.461$) or DLQI (7.20 and 5.88, $p=0.535$). Both EQ-5D and EQ VAS demonstrated a significant correlation with age ($r_s=-0.20$, $p=0.004$ and $r_s=-0.24$, $p=0.001$).

Among clinical subtypes, patients with palmoplantar psoriasis and psoriatic arthritis reported the worst health status (mean EQ-5D 0.36 and 0.48, EQ VAS 50.33 and 56.61, DLQI 11.42 and 9.26). The use of health services such as visits to a GP, hospitalisation and the necessity of home help were significant determinants of decreased HRQoL. Visits to dermatologist(s) in the last three months had no impact on HRQoL outcomes. Patients that used home help in the last month experienced particularly impaired HRQoL (mean EQ-5D 0.35). Patients treated with biologicals rated their HRQoL significantly better compared to those on either systemic non-biological, topical or no treatment (mean EQ-5D 0.75 vs. 0.63, EQ VAS 70.72 vs. 57.46 and DLQI 2.14 vs. 10.80, $p<0.001$ for all).

4.1.5 Subjective expectations on HRQoL for six months ahead

Out of the 200 patients who participated in the survey, answers of 167 were included in the analysis of expectations. Psoriasis patients expected to improve on average by 0.10±0.23 for their EQ-5D score within six months ($p<0.001$) *(Table 7*). Overall, 83 (49%) expected no change at all in any of the five dimensions of EQ-5D. Sixty-two (37%) and 22 (13%) patients expected increases and decreases in HRQoL, respectively. The mean EQ-5D score of those who expected better, same or worse HRQoL in six months were 0.52, 0.86 and 0.69, respectively ($p<0.001$). Those who expected amelioration expected more than a two-fold increase in the EQ-5D score (0.32) compared with those who expected a deterioration (-0.12). The most prominent improvement was expected in the dimensions of anxiety/depression and pain/discomfort (16% and 17% expected to reach the level of 'no problems', respectively).

Female gender, younger age, non-marital status, psoriatic arthritis, palmoplantar or inverse psoriasis, worse health state (measured by EQ-5D, DLQI or PASI), being at the initiation of first biological therapy or being treated by topical therapy were associated more often with optimistic expectations. On the contrary, older patients, those in a better health state (EQ-5D) and those with nail or scalp involvement tended to expect deterioration. The difference between actual and expected EQ-5D demonstrated a moderate inverse correlation with the actual EQ-5D and EQ VAS and a weak positive correlation with DLQI and PASI. The more severe the patients' current health state, the higher their expectations (*Table 8*).

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Table 6 Differences in HRQoL and disease severity between subgroups

	EQ-5D		EQ VAS		DLQI		PASI	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Gender								
Male	132	0.73 (0.31)*	135	65.10 (21.15)	134	5.88 (6.91)	137	8.14 (10.22)
Female	60	0.62 (0.31)*	61	62.94 (21.86)	60	7.20 (8.06)	63	7.72 (9.63)
Clinical subtypes								
Chronic plaque psoriasis	123	0.63 (0.32)*	126	60.17 (20.55)*	125	8.84 (7.23)*	126	11.70 (10.27)*
Erythrodermic psoriasis	4	0.71 (0.33)	4	62.25 (15.28)	4	10.25 (8.81)	4	20.40 (10.71)*
Guttate psoriasis	4	0.74 (0.08)	4	48.00 (10.16)	4	7.25 (5.06)	4	16.03 (7.89)*
Inverse psoriasis	17	0.55 (0.40)	17	54.12 (22.81)*	17	13.12 (6.37)*	18	21.83 (14.92)*
Nail psoriasis	68	0.62 (0.32)*	71	58.96 (20.22)*	71	10.00 (7.28)*	71	13.47 (10.55)*
Palmoplantar psoriasis	12	0.36 (0.39)*	12	50.33 (21.42)*	12	11.42 (6.82)*	12	18.38 (16.04)*
Psoriatic arthritis	56	0.48 (0.36)*	57	56.61 (20.76)*	57	9.26 (7.70)*	57	12.42 (11.47)*
Scalp psoriasis	67	0.62 (0.31)*	69	56.95 (19.55)*	69	12.42 (6.55)*	69	16.19 (10.71)*
Health services								
GP visit(s) in the last month**	47	0.47 (0.32)*	48	51.99 (20.58)*	48	11.21 (7.76)*	49	12.59 (10.74)*
Dermatologist visit(s) in the last three months	152	0.67 (0.32)	156	63.11 (21.19)	156	6.22 (7.48)	159	7.74 (10.07)
Hospitalisation(s) in the last 12 months **	54	0.59 (0.36)*	56	53.44 (21.91)*	56	10.05 (8.08)*	57	11.61 (9.64)*
Use of home help in the last month	27	0.35 (0.41)*	27	52.65 (21.43)*	27	13.70 (6.70)*	27	17.77 (12.40)*
Treatments								
No or topical therapy	32	0.65 (0.31)	32	54.50 (20.44)	32	12.22 (6.45)	36	18.43 (11.16)
Systemic non-biological therapy	58	0.62 (0.31)	61	59.01 (17.12)	61	10.05 (7.80)	61	11.19 (9.55)
Biological therapy	102	0.75 (0.31)*	103	70.72 (21.96)*	101	2.14 (3.92)*	103	2.50 (4.91)*

* Mann-Whitney U test or Kruskal-Wallis test $p<0.05$; ** due to psoriasis.

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Table 7 HRQoL expectations for six months ahead and future ages of 60 to 90

	N (%)	Actual EQ-5D	Expected EQ-5D score for six months ahead	Difference between actual score and six months expectations	Expected EQ-5D scores for future ages			
					60	70	80	90
N (response rate, %)	167 (100%)				114 (93%)	143 (88%)	119 (72%)	92 (55%)
Total sample	**167**	**0.71 (0.30)**	**0.81 (0.24)**	**0.10 (0.23)[a]**	**0.56 (0.48)**	**0.38 (0.50)**	**0.15 (0.55)**	**-0.17 (0.54)**
Gender								
Female	**49 (29%)**	0.62 (0.32)	0.80 (0.25)	0.18 (0.28) [a,b]	0.31 (0.60) [b]	0.27 (0.56)	0.06 (0.57)	-0.20 (0.56)
Male	**118 (71%)**	0.75 (0.28)	0.82 (0.24)	0.07 (0.20) [a,b]	0.66 (0.38) [b]	0.43 (0.46)	0.20 (0.54)	-0.16 (0.53)
Clinical subtypes [§, **]								
Chronic plaque psoriasis	**107 (64%)**	0.65 (0.30)	0.77 (0.26)	0.13 (0.25) [a]	0.48 (0.51) [b]	0.29 (0.53) [b]	0.07 (0.56) [b]	-0.26 (0.52) [b]
Inverse psoriasis	**15 (9%)**	0.61 (0.33)	0.89 (0.18)	0.28 (0.33) [a,b]	0.63 (0.43)	0.42 (0.62)	0.20 (0.58)	-0.11 (0.61)
Nail psoriasis	**59 (35%)**	0.63 (0.31)	0.76 (0.26)	0.13 (0.23) [a]	0.42 (0.53) [b]	0.25 (0.56) [b]	0.03 (0.59)	-0.21 (0.55)
Scalp psoriasis	**59 (35%)**	0.64 (0.29)	0.75 (0.29)	0.10 (0.21) [a]	0.45 (0.54)	0.21 (0.59) [b]	-0.01 (0.58) [b]	-0.20 (0.61)
Psoriatic arthritis	**48 (29%)**	0.51 (0.34)	0.70 (0.31)	0.19 (0.29) [a,b]	0.30 (0.57) [b]	0.16 (0.55) [b]	0.04 (0.55)	-0.17 (0.57)
Palmoplantar psoriasis	**9 (5%)**	0.48 (0.31)	0.75 (0.20)	0.27 (0.22) [b]	0.57 (0.36)	0.44 (0.33)	0.42 (0.29)	-0.04 (0.78)
Number of present clinical subtypes								
0 (asymptomatic at the time of the survey)	**47 (28%)**	0.87 (0.23)	0.92 (0.14)	0.05 (0.18)	0.76 (0.31)[b]	0.58 (0.34) [b]	0.33 (0.50) [b]	-0.02 (0.54)
1	**28 (17%)**	0.71 (0.26)	0.79 (0.22)	0.08 (0.25)	0.53 (0.50) [b]	0.37 (0.47) [b]	0.05 (0.52) [b]	-0.33 (0.42)
2-3	**70 (42%)**	0.67 (0.29)	0.80 (0.23)	0.13 (0.23) [a]	0.54 (0.47) [b]	0.36 (0.51) [b]	0.18 (0.55) [b]	-0.20 (0.55)
≥4	**22 (33%)**	0.49 (0.33)	0.66 (0.36)	0.17 (0.28) [a]	0.16 (0.59) [b]	0.03 (0.59) [b]	-0.13 (0.58) [b]	-0.24 (0.60)
Present treatment[***]								
Topical	**17 (10%)**	0.64 (0.34)	0.91 (0.16)	0.26 (0.33) [a]	0.91 (0.18) [b]	0.53 (0.48)	0.31 (0.56)	0.21 (0.66)
Systemic non-biological	**40 (24%)**	0.65 (0.29)	0.72 (0.23)	0.07 (0.19) [a]	0.40 (0.50) [b]	0.23 (0.53)	-0.04 (0.51)	-0.28 (0.55)
Biological	**94 (56%)**	0.76 (0.28)	0.84 (0.22)	0.08 (0.21) [a]	0.58 (0.47) [b]	0.41 (0.49)	0.22 (0.54)	-0.13 (0.51)
First biological is indicated at the time of the survey	**14 (8%)**	0.59 (0.34)	0.77 (0.37)	0.18 (0.27) [a]	0.47 (0.55) [b]	0.29 (0.49)	-0.02 (0.64)	-0.41 (0.45)
Expected survivors* (N, % of respondents)	-	-	-	-	109 (96%)	130 (90%)	62 (52%)	18 (20%)
Expected survivors	-	-	-	-	0.59 (0.46) [a]	0.48 (0.41) [a]	0.42 (0.41) [a]	0.22 (0.47) [a]
Expected non-survivors	-	-	-	-	-0.32 (0.32) [a]	-0.06 (0.61) [a]	-0.14 (0.53) [a]	-0.26 (0.51) [a]

a: Wilcoxon signed-rank test $p<0.05$; b: Mann-Whitney U test or Kruskal Wallis test $p<0.05$. § Combinations are possible. * Expected to live until the future age asked.
** Two patients had guttate or erythrodermic psoriasis. *** Two patients had received no therapy at the time of the survey.

Table 8 Correlations between expectations and continuous variables

	Expected EQ-5D in six months		**Expected length of life**		**Expected EQ-5D at the age of …**			
	EQ-5D in six months	Difference [expected in six months – actual EQ-5D]	Subjective LE	Difference [subjective – actual LE]	60 yrs	70 yrs	80 yrs	90 yrs
Age	-0.34*	-0.11	0.21*	-0.07	-0.20*	-0.02	0.09	0.03
Subjective LE	0.30*	-0.11	-	0.90*	0.43*	0.50*	0.55*	0.48*
Actual LE	-0.27*	0.03	0.14	-0.26*	0.33*	-0.12	-0.03	-0.04
Psoriasis duration	-0.31*	-0.09	0.06	-0.03	-0.29*	-0.11	-0.05	-0.04
EQ-5D	0.66*	-0.44*	0.35*	0.47*	0.62*	0.57*	0.52*	0.52*
EQ VAS	0.51*	-0.06	0.29*	0.36*	0.52*	0.43*	0.43*	0.38*
DLQI	-0.24*	0.18*	-0.20*	-0.20*	-0.16	-0.25*	-0.21*	-0.26*
PASI	-0.22*	0.18*	-0.12*	-0.14	-0.21*	-0.22*	-0.14	-0.20

* Spearman's correlation $p<0.05$. For EQ-5D and EQ VAS a higher score, for DLQI and PASI a lower score refers to a better health state.

4.1.6 Subjective expectations for life expectancy

The results related to subjective LE are presented in *Table 9*. Male and female patients expected to live until 74.86±9.54 and 80.09±1.77 years, respectively. For males we found an overestimation, while for females we uncovered an underestimation of the gender- and age-matched statistical LE. Palmoplantar involvement, inverse psoriasis, psoriatic arthritis and scalp psoriasis were responsible for the largest underestimations (-4.01, -3.01, -2.67, -1.65 years). Patients presenting four or more clinical subtypes, and those at the initiation of their first biological treatment, had very low expectations. Patients' age, EQ-5D, EQ VAS, DLQI and PASI scores correlated moderately or weakly with subjective LE (*Table 8*).

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Table 9 Difference between actual and expected life expectancy

	N (%)	Subjective LE	Actual LE	Difference subjective-actual LE
	167	76.21 (10.92)	75.82 (4.05)	0.39 (11.21)
Gender				
Female	**49 (29%)**	74.86 (9.54)	80.09 (1.77)	-5.23 (9.34) [a,b]
Male	**118 (71%)**	76.77 (11.43)	74.04 (3.34)	2.73 (11.14) [a,b]
Education				
Lower	**32 (19%)**	73.50 (13.50)	76.82 (3.69)	-3.32 (12.62)
Secondary	**98 (59%)**	75.57 (9.61)	75.50 (4.23)	0.07 (9.91)
College/university	**37 (22%)**	80.24 (11.29)	75.79 (3.82)	4.46 (11.25) [a]
Net monthly income (HUF)				
< 75,000	**62 (37%)**	75.29 (12.08)	76.44 (3.81)	-1.15 (12.52) [b]
75,001-150,000	**65 (39%)**	75.62 (9.66)	75.65 (4.25)	-0.03 (9.22) [b]
150,001-250,000	**21 (13%)**	79.00 (8.55)	75.64 (4.26)	3.36 (9.41) [b]
250,001-350,000	**11 (7%)**	84.09 (8.79)	74.58 (3.51)	9.51 (8.46) [a,b]
Clinical subtypes*				
Chronic plaque psoriasis	**107 (64%)**	75.75 (10.82)	75.89 (4.08)	-0.14 (11.15)
Inverse psoriasis	**15 (9%)**	74.53 (10.19)	77.55 (4.38)	-3.01 (8.69)
Nail psoriasis	**59 (35%)**	73.93 (11.18)	75.52 (3.86)	-1.59 (11.09)
Scalp psoriasis	**59 (35%)**	74.71 (11.34)	76.36 (4.29)	-1.65 (11.57) [b]
Psoriatic arthritis	**48 (29%)**	74.06 (10.32)	76.73 (3.60)	-2.67 (10.32)
Palmoplantar psoriasis	**9 (5%)**	73.89 (8.85)	77.90 (3.36)	-4.01 (8.44)
Number of present clinical subtypes				
0 (asymptomatic at the time of the survey)	**47 (28%)**	77.49 (11.61)	75.40 (4.15)	2.09 (11.99)
1	**28 (17%)**	78.43 (10.29)	76.11 (3.65)	2.32 (10.93)
2-3	**70 (42%)**	75.89 (10.32)	75.36 (4.16)	0.53 (10.42)
≥4	**22 (33%)**	71.68 (11.35)	77.80 (3.55)	-6.12 (10.65)[a]
Present treatment[§]				
Topical	**17 (10%)**	76.76 (8.02)	76.16 (4.28)	0.61 (7.41)
Systemic non-biological	**40 (24%)**	76.55 (11.25)	76.17 (4.22)	0.38 (12.14)
Biological	**94 (56%)**	76.51 (12.61)	75.36 (4.00)	1.15 (12.92)
Initiation of first biological at the time of the survey	**14 (8%)**	73.43 (7.06)	76.88 (3.65)	-3.45 (6.20)[a]

a: Wilcoxon signed-rank test $p<0.05$; b: Mann-Whitney U or Kruskal-Wallis test $p<0.05$.*Combinations are possible. ** Two patients had guttate or erythrodermic psoriasis. § Two patients had received no therapy at the time of the survey.

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4.1.7 Expectations for HRQoL at future ages

The age range of respondents answering questions concerning HRQoL expectations for older ages was roughly relevant to the sample, because 73%, 97%, 99% and 100% of the patients were below the ages asked (60-90), respectively (*Table 7*). Expected survivors rated their future EQ-5D at ages of 60 to 90: 0.59±0.46, 0.48±0.41, 0.42±0.41 and 0.22±0.47. While survivors scored positive EQ-5D scores at each given age, non-survivors scored on average negative, even for the age of 60. This finding is confirmed by the significant moderate correlation found between subjective LE and expected future EQ-5D scores (*Figure 8*). For each decade, the highest decline was expected in mobility and pain/discomfort dimensions of EQ-5D.

Males expected to have a better HRQoL at each future age, but this was only significant for the age of 60 ($p=0.005$). Future HRQoL expectations correlated moderately with current EQ-5D and EQ VAS. A weak inverse correlation was identified between future HRQoL and either DLQI or PASI (*Figure 8*).

4.1.8 Comparison of HRQoL expectations with the general population

HRQoL expectations for future decades were compared to findings from the age-matched participants of a similar study of the Hungarian general population (*Figure 9*) [165]. The expectations of psoriasis patients are considerably lower than those of the general population in Hungary. However, for the age of 70, actual EQ-5D values of the age-matched patients within the sample substantially exceeded expectations (0.73 vs. 0.38).

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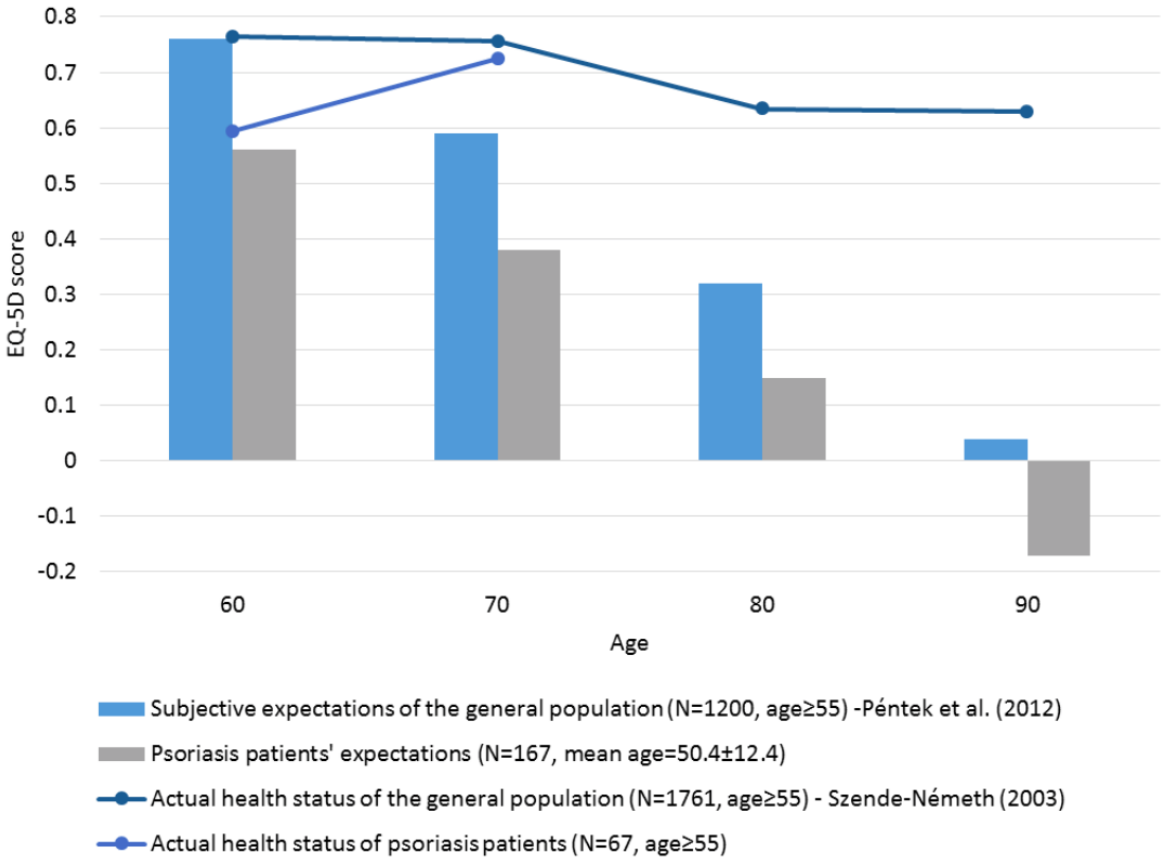

Figure 9 Comparison of subjective HRQoL expectations in EQ-5D for older ages between psoriasis patients and the general population

General population and psoriasis patients between the ages of 55-64, 65-74, 75-84 and 85-94 represent the age categories of 60, 70, 80 and 90, respectively. The results for psoriasis patients aged 75 or more are not depicted here, as there was only one patient over the age of 75.

Data sources: Péntek et al. 2012 [165], Szende-Németh 2003 [118]

4.2 Pemphigus study

4.2.1 Systematic review

4.2.1.1 Characteristics of included studies

The search strategy identified 612 records. *Appendix 12.3* presents the PRISMA flowchart used in the selection process [182]. After removing duplicates, 368 records were screened on title and abstract. Out of the 35 papers remaining for full-text review, 21 were excluded based on predefined exclusion criteria. Screening references yielded two more papers that were not indexed in electronic databases but met the inclusion and exclusion criteria. Thus, in total, 16 studies were included in the systematic review.

The main findings of the 16 papers are summarised in *Table 10* [183-198]. Studies originated from eight different countries: Italy (n=5) [190, 191, 193-195], Iran (n=4) [183-185, 187], India (n=2) [186, 192], Japan (n=1) [188], Germany (n=1) [189], Poland (n=1) [198], Morocco (n=1) [196] and Brazil (n=1) [197].

There were 11 cross-sectional studies [183, 185-190, 192-195], four case-control studies [189, 191, 196, 198] and one prospective cohort with a four-month follow-up period [197]. The patient populations varied between seven and 380 patients, with only five studies enrolling >100 participants [183, 188, 190, 191, 195]. The 16 studies involved a total of 1,465 patients, of whom 966 (66%) had PV. Besides PV, the following types of pemphigus occurred: 123 PFo, 41 seborrheic, eight vegetans, two IgA and two paraneoplastic. The clinical type of 323 (22%) patients was unknown or not specified. The mean age of the included patients ranged between 39.3 and 61.6 years (n=12) [183, 185, 187-192, 195-198], and the rate of males varied from 37% to 80% (n=13) [183-192, 195, 196].

Two studies recruited only newly diagnosed or untreated patients [183, 185], five enrolled patients on adjuvant and/or corticosteroid therapy [184, 186, 190, 191, 196] and a small study investigated the impact of physiotherapy on HRQoL [197].

4.2.1.2 HRQoL measures used in pemphigus

Four types of HRQoL instruments were used: Short form-36 (SF-36), Activities of Daily Livings (ADLs), World Health Organization Quality of Life-BREF (WHOQOL-BREF), and World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). Four different dermatology- or oral disease-specific measures were applied: Dermatology Life Quality Index (DLQI), Skindex-29, Skindex-17, and Chronic Oral Mucosal Diseases Questionnaire (COMDQ). Among these, SF-36 (n=8), DLQI (n=5) and Skindex-29 (n=4) were the most frequent.

Furthermore, half of the studies applied at least one psychological/psychiatric measure, the most common of which was the General Health Questionnaire (GHQ)-12 or -28 (n=7) [183, 185, 186, 190, 191, 193, 195].

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Table 10 Pemphigus HRQoL studies identified

Author, year	Country, study period	Study type	Patients' characteristics	HRQoL measures	HRQoL scores (mean)	Determinants of decreased HRQoL
Sakuma, 2000[188]	Japan Sep.-Dec. 1997	cross-sectional	n=380 (PV 239, foliaceus 80, seborrheic 31, vegetans 6, other 6, unknown 18), 78.7% in remission, 69% treated for > 2 years Males: 39% Mean age: males 58.1, females 52.5 years	ADLs	Rate of patients: bathe alone 96.5%; use the toilet alone 99.7%; eat alone 99.7%; pain while eating or swallowing 40.4%; cook alone 85.2%; shave or make-up alone 97.0%; use public transport alone 90.8%; drive a car 82.3%	-
Terrab, 2005[196]	Morocco Jan.-Aug. 2002	case-control	n=30 (PV 14, seborrheic 10, foliaceus 4, vegetans 2), 70% corticosteroid, 30% adjuvant (+corticosteroid) treatment Males: 20% Mean age: 44.6 years	SF-36	PF 59.5; RP 10.0; BP 57.0; GH 48.6; VT 35.5; SF 43.7; RE 8.8; MH 40.4	Profession, Face involvement Extent of lesions
Mayrshofer, 2005[189]	Germany Nov. 1997-Jan. 2002	cross-sectional	n=27 PV, newly diagnosed Males: 40% Mean age: 55.9 years	DLQI	10.0±6.7, symptoms 1.4; self-confidence 1.6; shopping and housekeeping 1.0; clothing 0.9; leisure 1.3; sport 0.6; work and school 0.9; relationships 1.0; sexuality 0.6; treatment 1.0.	-
Tabolli, 2006[193]	Italy Feb.-May 2005	cross-sectional	n=13 (type not specified) Males: NR Mean age: NR	SF-36	PF 57.7; RP 34.1; BP 55.8; GH 51.0; VT 55.0; SF 52.9; RE 60.6; MH 50.8	-
				Skindex-29	symptoms 47.3; emotions 46.7; social functioning 40.5	
Tabolli, 2008[194]	Italy Jan.-June 2006	cross-sectional	n=58 (PV 51, foliaceus 7), 75% in-patients Males: 43% Mean age: NR	SF-36	P. vulgaris: PF 72; RP 43; BP 63; GH 49; VT 49; SF 61; RE 47; MH 53	PGA >4 Disease duration ≥ 5 years ASQ or CDQ≥8 Mucocutaneus lesions

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Author, year	Country, study period	Study type	Patients' characteristics	HRQoL measures	HRQoL scores (mean)	Determinants of decreased HRQoL
					P. foliaceus: PF 79; RP 46; BP 66; GH 48; VT 63; SF 65; RE 62; MH 61	
Darjani, 2008[184]	Iran April –July 2005	case-control	n=76 (type not specified), corticosteroid or adjuvant (+corticosteroid) treatment Males: 42.3% Mean age: 31.6% 40-49 years	SF-36	PF 71.9; BP 74.0; RP 55.8; RE 69.9; VT 59.0; GH 59.0; SF 90.1; MH 69.4	Older age Longer disease duration Lower education level Job Repeated hospitalisations Treatment with adjuvant (+corticosteroid)
Paradisi, 2009[191]	Italy Feb. 2007-Feb. 2008	case-control	n=126 (PV 112, foliaceus 10, paraneoplastic 2, IgA pemphigus 2), corticosteroid and/or adjuvant therapy Males: 53% Mean age: 52.2 years	SF-36	P. vulgaris: PF 73; RP 45; BP 61; GH 49; VT 53; SF 62; RE 49; MH 56; PCS 43; MCS 37. P. foliaceus: PF 65; RP 47; BP 56; GH 47; VT 46; SF 57; RE 60; MH 56, PCS 39; MCS 38.	Age > 50 Female PGA >1 Ikeda >3 Comorbidities≥2** Treatment with ≤10 mg/day corticosteroids
				Skindex-29	P. vulgaris: symptoms 36; emotions 36; social functioning 32 P. foliaceus: symptoms 52; emotions 46; social functioning 52	Female PGA >1 Ikeda >3 PV
Timoteo, 2010[197]	Brazil NR	prospective cohort (4-month follow up)	n=7 (type not specified), treated with physiotherapy Males: 80% of the total sample (n=15) Mean age: 40 years (n=15)	SF-36	Physiotherapy improved HRQoL after 4 months in all dimensions of SF-36 except for VT and SF (results reported graphically)	Physiotherapy
Arbabi, 2011[183]	Iran Apr. 2004-June 2008	cross-sectional	n=212, (PV 206, foliaceus 6), 56% newly diagnosed Males: 42% Mean age: 44.9 years	DLQI	Total: 13.8, new patients 12.8, patients with recurrent attack 15.9	GHQ-28 Recurrence of pemphigus

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Author, year	Country, study period	Study type	Patients' characteristics	HRQoL measures	HRQoL scores (mean)	Determinants of decreased HRQoL
Paradisi, 2012[190]	Italy Feb. 2007-Feb. 2009	cross-sectional	n=113 (PV 103, foliaceus 10), 70% traditional adjuvant, 20% rituximab Males: 37% Mean age: 50 years	SF-36	PCS 42.8; MCS: 37.8	GHQ-12 Not receiving adjuvant therapy
				Skindex-29	symptoms 33.9; emotions 34.8; social functioning 31.7	GHQ-12
Ghodsi, 2012[185]	Iran July 2005-June 2006	cross-sectional	n=61 PV, newly diagnosed Males: 38% Mean age: 44.1 years*	DLQI	Total: 10.9 ± 6.9, symptoms and feelings 2.8; daily activities 2.2; leisure 1.8; work and school 1.5; personal relationships 1.6; treatment 1.1	Nasal or pharynx involvement Positive Nikolsky's sign Higher severity Itching Skin burning Longer disease duration
Layegh, 2013[187]	Iran NR	cross-sectional	n=78 PV, 32% newly diagnosed Males: 40% Mean age: 46.98 years	DLQI	Total: new patients 12.7 ± 6.4, patients with longer disease duration 7.7 ± 7.2	Hospitalised and newly diagnosed cases
Wysoczyńska, 2013[198]	Poland 2010-2012	case-control	n=22 (PV 18 and foliaceus 4), 59% of patients had disease duration >5 years Males: NR Mean age: 61.6 years	SF-36	Total: 54.1; PCS 55; MCS 53; RP 12.5; RE 33.3[§]	Higher severity Physical symptoms (not specified)
				DLQI	Total: 4.0 ± 5.9	Higher severity Physical symptoms (not specified)
				Skindex-29	Total: 56.0 ± 23.4	Higher severity Physical symptoms (not specified)
Kumar, 2013[186]	India July 2006-Sep. 2007	cross-sectional	n=50 (PV 48, foliaceus 2, corticosteroid +adjuvant therapy) Males: 58% Age: 52% aged 35-54 years*	WHOQOL-BREF	Total: 44.8 ± 4.8; physical health 10.8; psychological health 12.0; relationships 7.8; environment 14.1	*Physical health:* Ikeda, concurrent psychiatric illness, WHODAS 2.0, ATT, AI, MADSR, IMPACT *Psychological health:* disease severity, concurrent psychiatric

Author, year	Country, study period	Study type	Patients' characteristics	HRQoL measures	HRQoL scores (mean)	Determinants of decreased HRQoL
						illness, WHODAS 2.0, AI, MADSR, IMPACT
				WHODAS 2.0	Total: 42.2 ± 25.0	Ikeda, concurrent psychiatric illness, WHODAS 2.0, AI, ATT, MADSR, IMPACT, SSQ
Tabolli, 2014[195]	Italy 2012-2013	cross-sectional	n=203 (type not specified) Males: 42% Mean age: 52.7 years	Skindex-17	symptoms - with lesions 36.4, without lesions 25.6; psychosocial - with lesion 42.4, without lesions 32.9	Female Presence of skin lesions
Rajan, 2014[192]	India Nov. 2011-Feb. 2012	cross-sectional	n=9 PV Males: 56% Mean age: males 44.8, females 39.3 years	COMDQ	Total: 73.6 ± 5.6; pain and functional limitation 25.7; medication and treatment 17.6; social and emotional 22.3; patient support 8.3	-

* Ghodsi, 2012[185]: inclusion > 12 years; Kumar, 2013[186]: inclusion ≥15 years

§ In the study of Wysoczyńska, 2012 [198] mean scores of the other six dimensions of SF-36 were not reported.

** most common comorbidities in the study: hypertension, osteoporosis, diabetes, obesity, glaucoma

NR: not reported

For SF-36 and WHOQOL-BREF higher scores refer to a better HRQoL, and for any other measures higher scores represent a worse HRQoL.

ADLs = Activities of Daily Livings; AI = Anxiety Index; ASQ = Anxiety Scale Questionnaire; ATT = Attitude to Appearance scale; BP = bodily pain; CDQ = Clinical Depression Questionnaire; COMDQ = Chronic Oral Mucosal Diseases Questionnaire; DLQI = Dermatology Life Quality Index; GH = general health; GHQ = General Health Questionnaire; HRQoL = health-related quality of life; IMPACT = Impact of Skin Disease Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; MH = mental health; PF = physical functioning; PGA = Physician's Global Assessment on disease severity; PV = pemphigus vulgaris; RE = role-emotional; RP = role physical; SF = social functioning; SF-36 = Short form-36; SSQ = Social Support Questionnaire; VT = vitality; WHOQOL-BREF = World Health Organization Quality of Life-BREF; WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.

4.2.2 Results of the meta-analyses

4.2.2.1 Meta-analysis of studies with SF-36

Five studies were included in the meta-analysis, and all reported SF-36 dimension scores on treated and/or hospitalised pemphigus patients [184, 191, 193, 194, 196]. The studies of Paradisi et al. (2012) [190] and Wysonczyńska et al. [198] were not included in the meta-analysis, because they did not report results for each dimension of the SF-36. The study of Timoteo et al. [197] was excluded, as it only reported results graphically. The meta-analysis showed the highest deterioration in the role-physical dimension of SF-36 (38.1, 95% CI 20.4-55.9), followed by role-emotional (47.5, 95 % CI 21.9-73.2), vitality (50.7, 95% CI 43.6-57.7) and general health (51.5, 95% CI 45.9-57.0) (*Figure 10*).

4.2.2.2 Meta-analysis of studies with DLQI

Five studies reported a DLQI score in pemphigus patients, with mean scores sitting between 4.0 and 13.8 [183, 185, 187, 189, 198]. Four studies were included in the meta-analysis, all of which enrolled newly diagnosed or untreated pemphigus patients [183, 185, 187, 189]. Patients in the study by Wysonczyńska et al. were not included in the meta-analysis due to 77% of the participants reporting a disease duration of more than two years [198]. Newly diagnosed or untreated patients scored on average 12.0 (95% CI 11.1-12.9) (*Figure 11*).

4.2.2.3 Meta-analysis of studies with Skindex-29

Three studies reported the Skindex-29 dimension scores of medically treated and/or hospitalised pemphigus patients [190, 191, 193]. The meta-analysis indicated similar mean scores in the symptoms (35.8, 95% CI 32.7-38.9) and emotions (36.5, 95% CI 33.8-39.2) domains of Skindex-29, whereas they were slightly lower in social functioning (32.8, 95% CI 29.9-35.6) (*Figure 12*).

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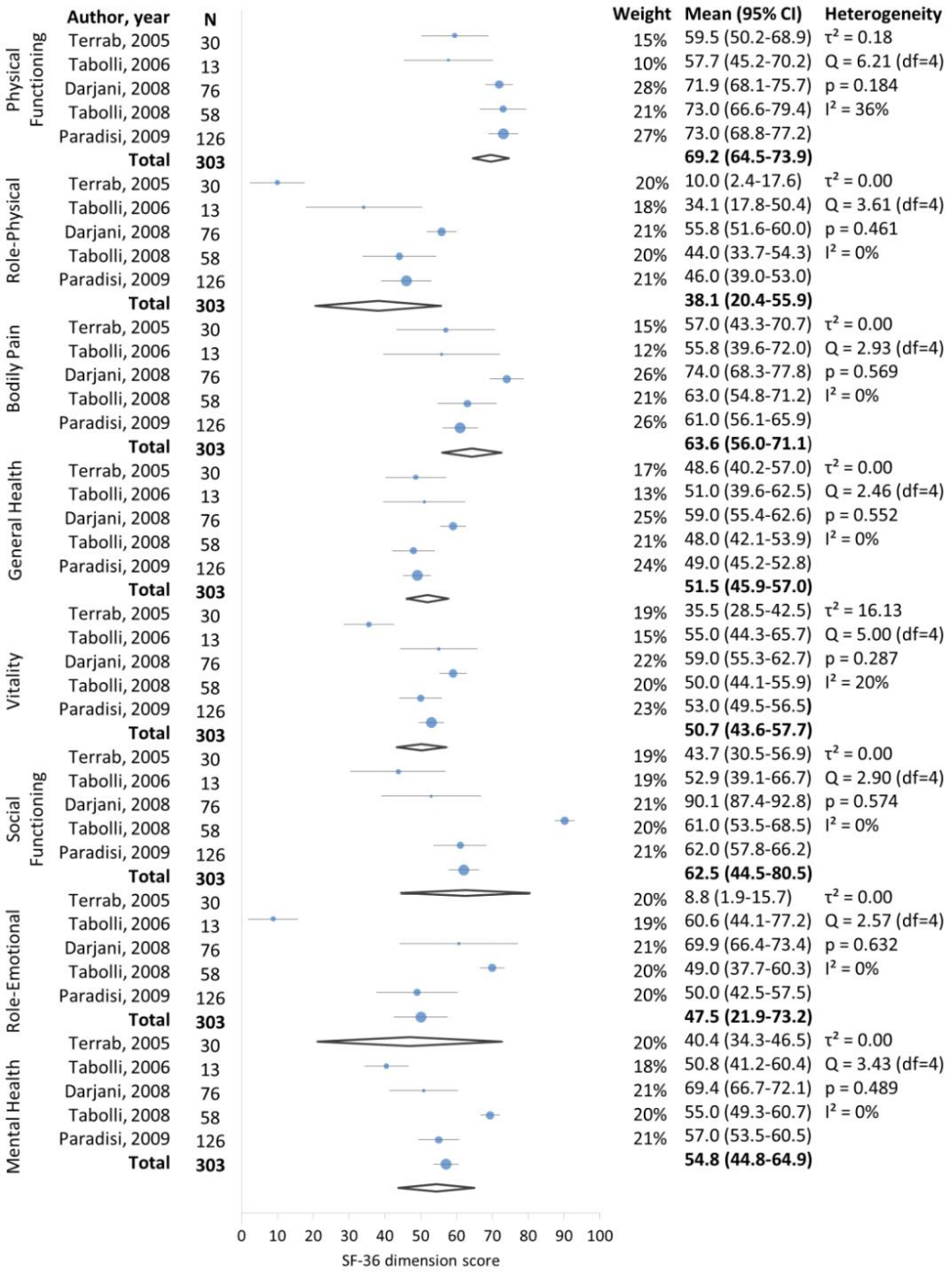

Figure 10 Meta-analysis of SF-36 studies in pemphigus patients

Random-effects models. Sizes of dots refer to the sample sizes of studies. All studies included treated and/or hospitalised pemphigus patients. SF-36 scores range from 0 (worse HRQoL) to 100 (better HRQoL).

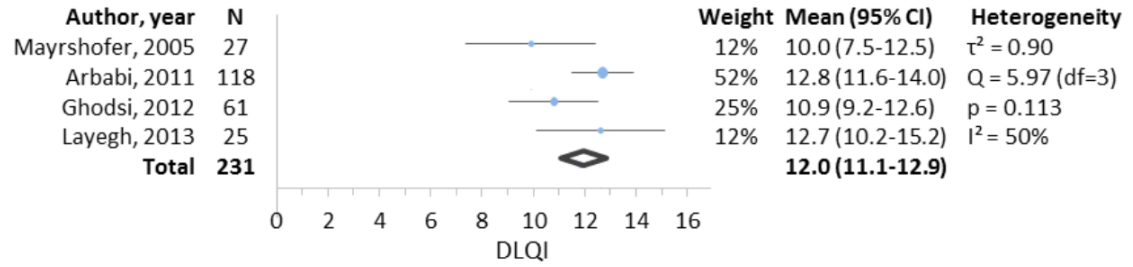

Figure 11 Meta-analysis of DLQI studies in pemphigus patients

Total DLQI scores of newly diagnosed or untreated pemphigus patients. Fixed-effects model. DLQI ranges from 0 to 30, where higher scores refer to worse HRQoL. Sizes of dots refer to the sample sizes of studies.

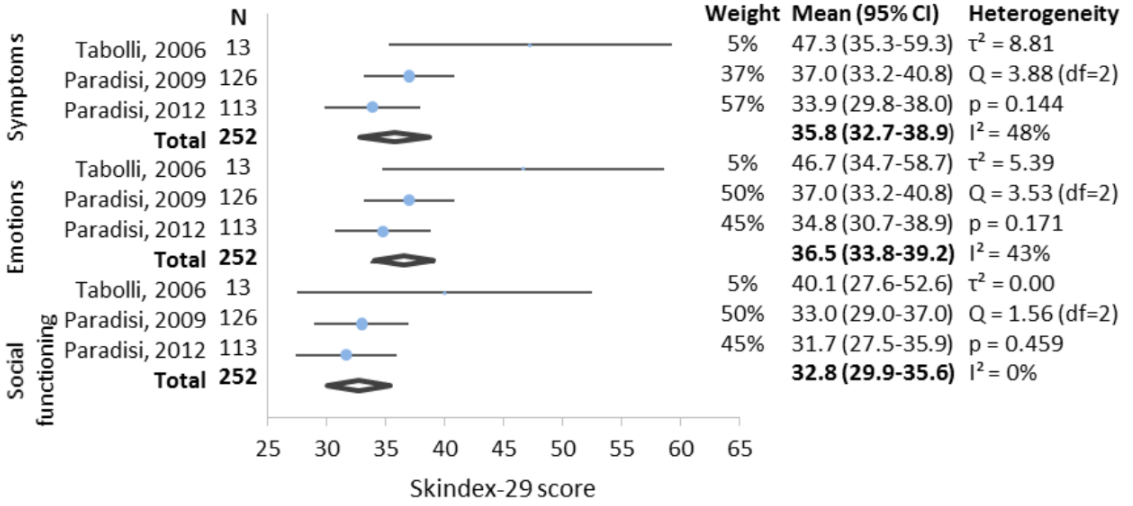

Figure 12 Meta-analysis of Skindex-29 studies in pemphigus patients

Skindex-29 dimension scores of medically treated and/or hospitalised pemphigus patients. A random-effects model was used in the symptoms dimension, whereas a fixed-effects model was employed in the emotions and social functioning dimensions. Scores range from 0 to 100, where higher scores refer to a worse HRQoL. Sizes of dots refer to the sample sizes of studies.

4.2.3 Determinants of HRQoL in pemphigus

Overall, 41 possible determinants of HRQoL in pemphigus were identified, which we classified into socio-demographic, clinical, treatment-related and psychological factors (*Table 11*).

Socio-demographic factors

Paradisi et al. found that older patients tended to have a decreased HRQoL in the RP, BP and RE dimensions of SF-36 and, according to Darjani et al., in total SF-36 scores [184,

191]. In contrast, no association between age and any SF-36 or Skindex-29 dimensions or DLQI was found in other studies [183, 185, 187, 191, 194, 196].

Female patients were found in a significantly worse HRQoL in all dimensions of SF-36, with the exception of RP and RE, and in the symptoms and emotions domain of Skindex [191, 195]. Another study conducted with SF-36 [194, 196] and three others with DLQI reported that gender had no significant effect on HRQoL [183, 185, 187].

In one study, lower educated patients reported decreased HRQoL in SF-36 [184]. In contrast, three other studies observed no relationship between the level of education and DLQI or SF-36 scores [185, 187, 194]. Two studies described that patients' jobs or professions influenced SF-36 scores [184, 196]. For example, Darjani et al. found that among pemphigus patients in Iran, housekeepers had the worst and farmers had the best HRQoL measured by SF-36 [181]. Three studies found that marital status was not associated with HRQoL [185, 194, 196].

Clinical factors

Worse HRQoL in SF-36 was linked to longer disease duration, especially in the VT, SF, RE and MH domains of SF-36 and in the total DLQI score [183-185, 194]. This is supported by the findings of Arbabi et al., who found that patients with recurrent pemphigus had significantly higher DLQI scores [183]. Other studies contradict this conclusion, when reporting no relationship between disease duration and HRQoL on DLQI, SF-36, Skindex-29 or WHOQOL-BREF [183, 186, 191, 196].

Patients with two or more somatic comorbidities had a lower HRQoL in all dimensions of SF-36 apart from SF [191]. A negative relationship between disease severity and HRQoL was described in five studies by SF-36, WHOQOL-BREF and Skindex-29 [185, 186, 191, 194, 198]. In contrast, the severity of the oral lesions in PV patients did not have a significant impact on DLQI [185]. The extension of the skin lesions was found in SF-36 to be a significant predictor of social functioning [196]. However, Mayrshofer et al. identified no association between the extension of the lesions and DLQI [189].

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Table 11 Determinants of HRQoL in pemphigus patients

Determinants of HRQoL	Number of studies	Total number of patients	Negative impact	No impact	Positive impact	References
Socio-demographic factors						
Older age	7	641	2	6	0	[183-185, 187, 191, 194, 196]
Female gender	7	768	2	5	0	[183, 185, 187, 191, 194-196]
Lower level of education	4	273	1	3	0	[184, 185, 187, 194]
Employment	**2**	**106**	**2**	**0**	**0**	[184, 196]
Marital status	3	149	0	3	0	[185, 194, 196]
Clinical factors						
Longer disease duration	7	613	3	4	2	[183-186, 191, 194, 196]
Higher disease severity	**5**	**317**	**10**	**0**	**0**	[185, 186, 191, 194, 198]
Oral severity	1	61	0	1	0	[185]
Clinical activity or presence of lesions	2	233	1	1	0	[195, 196]
Comorbidities	1	126	1	0	0	[191]
Extension of the lesions	2	57	1	1	0	[189, 196]
Facial localisation	1	30	1	0	0	[196]
Nasal or nasopharyngeal localisation	1	61	1	0	0	[185]
Mucocutaneus lesions	3	245	2	1	0	[185, 191, 194]
Itching	2	88	1	1	0	[185, 189]
Skin burning	2	88	1	1	0	[185, 189]
Pain	1	61	0	1	0	[185]
Physical symptoms (not specified)	1	22	3	0	0	[198]
Pemphigus foliaceus	2	184	0	2	1	[191, 194]
Positive Nikolsky's sign	1	61	1	0	0	[185]
Recurrent pemphigus	1	212	1	0	0	[183]
Number of hospitalisations	1	76	1	0	0	[184]
Inpatient	1	78	1	0	0	[187]
Average days spent in hospital	1	30	0	1	0	[196]
Complications due to pemphigus	1	30	0	1	0	[196]
Iatrogenic complications	1	30	0	1	0	[196]
Treatment-related factors						
Adjuvant (+ corticosteroid) vs. corticosteroid	4	345	1	3	2	[184, 190, 191, 196]

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Determinants of HRQoL	Number of studies	Total number of patients	Negative impact	No impact	Positive impact	References
Rituximab (+corticosteroid) vs. corticosteroid	1	113	0	0	1	[190]
Duration of systemic corticosteroid treatment	1	30	0	1	0	[196]
Use of other treatment in addition to adjuvant (+corticosteroid)	1	30	0	1	0	[196]
Physiotherapy	1	7	0	0	1	[197]
Monthly cost of treatment during active phase of pemphigus	1	30	0	1	0	[196]
Early termination of therapy due to the lack of financing	1	30	0	1	0	[196]
Psychological / psychiatric factors						
Concurrent psychiatric disorder	1	50	1	0	0	[186]
General Health Questionnaire positivity	**2**	**325**	**3**	**0**	**0**	[183, 195]
Anxiety	**2**	**108**	**2**	**0**	**0**	[186, 194]
Depression	**2**	**108**	**2**	**0**	**0**	[186, 194]
Behaviour after the onset of illness	1	50	1	0	0	[186]
Attitude to appearance	1	50	1	0	0	[186]
Social support	1	50	1	0	0	[186]
Coping strategy	1	50	0	1	0	[186]

The column listing ‘number of studies’ does not always equal the sum of the columns stating ‘negative/no/positive impact’. Bold font rows indicate a clearly significant relationship between a certain determinant and HRQoL noticed in at least two separate studies.

According to Terrab et al., there was no relationship between disease activity and any of the SF-36 dimensions [196], while in another study the presence of the lesions showed a significant impact on both the symptoms and psychosocial dimensions of Skindex-17 and on the GHQ-12 score [195]. Amongst symptoms, itching and skin burning showed significant effects on DLQI in one study but not in another [185, 189]. The presence of pain did not influence adversely the DLQI, but a positive Nikolsky-sign did [185].

Two studies compared HRQoL between PV and PFo patients [191, 194]. Paradisi et al. found a significantly worse health state of PV patients in the symptoms dimension of Skindex-29; nevertheless, this was not confirmed by SF-36 scores in this study, or by Tabolli et al. [191, 194].

Mucocutaneous lesions in PV patients were associated with a lower level of HRQoL, as assessed by SF-36, especially in the RE, RP and BP domains [191, 194]. By contrast, no such relationship between mucocutaneous lesions and total DLQI score was proven [185]. Patients with face involvement showed significantly deteriorated total SF-36 scores, and those with nasal or pharyngeal involvement indicated worse DLQI scores [185, 196].

Hospitalised patients reported higher total scores on DLQI [187]. Furthermore, in one study, the higher number of hospitalisations was associated with lower SF-36 total scores [184]. Yet, in another study, no relationship was found between the average length of hospitalisations and SF-36 [196].

Treatment-related factors

Compared to receiving no treatment or only corticosteroids, patients treated by corticosteroid therapy plus traditional adjuvants (e.g azathioprine, cyclophosphamide, mycophenolate mofetil) showed significantly improved SF-36 total scores in the study of Darjani et al. but a significant deterioration in the PF domain of SF-36 in the study of Paradisi et al. [184, 191]. In contrast, no such difference in SF-36 outcomes was noted between treatment groups in two other studies [190, 196]. With respect to Skindex-29, one study reported significantly better scores in the SF domain in patients receiving corticosteroids plus adjuvants, whereas in another study no significant difference was present [190, 191].

Patients who were treated with rituximab showed significantly higher SF-36 scores in the RP, VT and MH domains of SF-36 compared to those receiving only corticosteroids [190]. In the study of Timoteo et al. seven patients receiving physiotherapy improved HRQoL after four months in all dimensions of SF-36 except for VT and SF [197]. Neither the duration of systemic corticosteroid therapy nor the use of other treatments, cost of therapy or early termination of treatment due to financial issues had an impact on SF-36 scores [196].

Psychological factors

The presence of skin lesions compared to quiescent periods or a higher DLQI score were associated with the General Health Questionnaire (GHQ) positivity in two studies [183, 195]. Moreover, patients indicating higher a level of anxiety and depression had significantly lower HRQoL scores in both the physical and the psychological domains of WHOQOL-BREF and in all dimensions of SF-36, apart from BP (anxiety and depression) and PF (anxiety) [186, 194]. Kumar et al. observed that concurrent psychiatric illness, behaviour after illness, attitude to appearance and social support all influenced WHOQOL-BREF scores, but coping strategy did not [186].

4.2.4 Valuation of pemphigus health states by the general population

4.2.4.1 Characteristics of the pemphigus study population

Overall, 115 adults were recruited to the study, three of whom refused to participate in the group interviews. Thus 112 questionnaires were completed, of which the TTO tasks of four questionnaires were returned blank. Data from 108 respondents were therefore analysed. The mean age of the subjects was 26.0±9.1, and there were slightly more females (58%) than males (*Table 12*). Three-quarters of the participants were university students. There were no pemphigus patients in the sample, and 97% of the study population had never heard about pemphigus.

Table 12 Characteristics of the general population sample for the pemphigus study

	N (%) or Mean (SD)
Number of respondents	108
Gender	
Female	63 (58%)
Male	45 (42%)
Age (years)	26.0 (9.1)
Education	
Secondary school	24 (22%)
College/university	84 (78%)
Employment*	
University student	81 (75%)
Full-time job	29 (27%)
Part-time job	26 (24%)
Retired	2 (2%)
Other	5 (5%)
Prior experiences with pemphigus	
Have never heard about it	105 (97%)
Have read about it on the Internet	1 (1%)
Know someone with pemphigus	1 (1%)
Have seen pemphigus patients	1 (1%)
Have ever been diagnosed with pemphigus	0 (0%)

*combinations may occur

4.2.4.2 Visual analogue scale and time trade-off utility results

The mean estimated VAS scores attached to the PV, PFo and uncontrolled pemphigus health states were as follows: 0.25±0.15, 0.37±0.17 and 0.63±0.16, respectively (*Table 13*). Corresponding mean TTO utilities were 0.34±0.38, 0.51±0.32 and 0.75±0.31. The distribution of TTO utilities is presented in *Figure 13*.

Overall, 14% and 6% considered PV and PFo as being worse than dead (utility ≤ 0). The rate of '1' answers was very low for both the PV and PFo health states but as high as 26% for controlled pemphigus. There were no non-traders in this study (who rated all health states equal to 1). Significant differences were found in both the VAS and TTO utilities for all three health states ($p<0.001$). In each health state, TTO utilities were significantly higher compared to VAS ($p<0.001$).

Table 13 VAS and TTO utilities for pemphigus health states

	n	Mean (SD)	Median	Range (min-max)	utility ≤ 0	utility = 1
VAS*						
Uncontrolled PV	107	0.25 (0.15)	0.20	0-0.80	6 (6%)	0 (0%)
Uncontrolled PFo	107	0.37 (0.17)	0.35	0-0.90	1 (1%)	0 (0%)
Controlled pemphigus (either PV or PFo)	107	0.63 (0.16)	0.70	0.25-0.99	0 (0%)	0 (0%)
TTO						
Uncontrolled PV	108	0.34 (0.38)	0.40	(-1) - 1	15 (14%)	1 (1%)
Uncontrolled PFo	108	0.51 (0.32)	0.50	(-1) - 1	6 (6%)	4 (4%)
Controlled pemphigus (either PV or PFo)	108	0.75 (0.31)	0.80	(-1) - 1	2 (2%)	28 (26%)
TTO - inconsistent answers removed*						
Uncontrolled PV	104	0.35 (0.38)	0.40	(-1) - 1	13 (12%)	1 (1%)
Uncontrolled PFo	106	0.51 (0.32)	0.50	(-1) - 1	5 (5%)	4 (4%)
Controlled pemphigus (either PV or PFo)	107	0.75 (0.30)	0.80	(-1) - 1	2 (2%)	28 (26%)

All three health states differed statistically significantly (Wilcoxon signed-rank test $p<0.001$) measured by either VAS or TTO.

*VAS utilities in this study range between 0 (worst) and 1 (best).

**TTO utilities in this study range between -1 (worst) and 1 (best).

PFo = pemphigus foliaceus; PV = pemphigus vulgaris; TTO = time trade-off; VAS = visual analogue scale

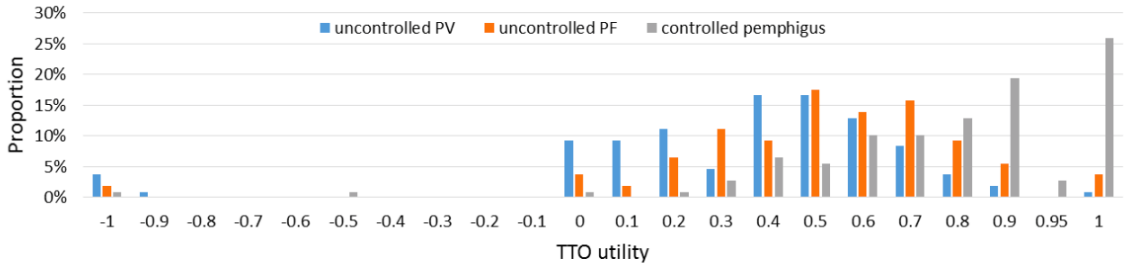

Figure 13 Distribution of TTO utilities for the pemphigus health states

PFo = pemphigus foliaceus; PV = pemphigus vulgaris; TTO = time trade-off
TTO utilities in this study are ranging between -1 (worst) and 1 (best).

Male gender and older age were associated with significantly higher utilities for PFo on VAS (0.42 vs. 0.34, p=0.024 and r=0.25, p=0.008), but this was not the case for PV or controlled pemphigus. More educated respondents tended to elicit higher utilities in PFo VAS (0.39 vs. 0.30, p=0.013), PFo TTO (0.54 vs. 0.39, p=0.032) and in PV VAS (0.26 vs. 0.20, p=0.027). Age or gender had no influence on the TTO responses, and employment status had no impact on either VAS or TTO utilities.

Seven inconsistent answers occurred which were linked to five respondents. The most common reason for inconsistency (n=5) was that more than one indifference point was marked on the response sheet, with gaps between them (*Appendix 12.4*). In one case, a respondent stopped trading life years and refused further trading, then returned to the 'cannot decide' option (n=1). In yet another case, a participant continued to trade life years after reaching the point of indifference (n=1). After the removal of inconsistent answers, there were almost no changes in the results (*Table 13*).

4.3 DLQI study

4.3.1 Characteristics of the DLQI study population

A total of 516 responses were collected in the Internet survey. Overall, 208 participants were excluded for the following reasons:

- 15 participants were under the age of 18 years;
- 175 returned the TTO part of the questionnaire blank;
- 18 provided inconsistent answers in all three DLQI health states.

The responses of 308 respondents were judged valid and included in the analyses. The mean age of the study population was 27.4 (min.-max. 18-75) years, with a female predominance (69%) (*Table 14*). Almost half of the respondents reported to hold a college or university degree (47%). Overall, 18% of the participants responded to have had a dermatological condition diagnosed by a physician at the time of the survey. Non-atopic dermatitis (4%), acne (3%) and psoriasis (2%) were among the most frequent diagnoses.

4.3.2 Time trade-off utility values

Overall, 124 to 130 individuals assessed each health state, and a total of 882 utilities were elicited (*Table 15*). Mean utilities for the six-point M1, M2, M3 health states were as follows: 0.64±0.32, 0.75±0.27 and 0.62±0.30. Mean utilities for the 11-point health states were U_{L1}=0.66±0.31, U_{L2}=0.64±0.28 and U_{L3}=0.59±0.29. Health state ‘S’ was assessed the most severe with a mean U_S=0.56±0.29 (*Figure 14*). The six-point ‘M1’ was valued as bad as being dead (i.e. utility=0) by 12% of the respondents, while this rate was only 5% for ‘M2’. Over 22% of the respondents were not willing to trade time for health state ‘M2’ (i.e. utility=1). In contrast, this rate was a mere 10% for health state ‘S’.

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Table 14 Characteristics of the DLQI study population

	N (%) or Mean (SD)
Number of respondents	308 (100%)
Gender (missing n=2)	
Female	210 (68.6%)
Male	96 (31.4%)
Age (years) (missing n=1)	27.4 (10.3)
Education (missing n=2)	
Primary school	1 (0.3%)
Secondary school	160 (52.3%)
College/university	145 (47.4%)
Employment*	
University student	177 (57.5%)
Full-time job	104 (33.8%)
Part-time job	48 (15.6%)
Unemployed	4 (1.3%)
Retired	3 (1.0%)
Other	16 (5.2%)
Medically diagnosed dermatological condition at the time of the survey (missing n=1)*	
No	253 (82.4%)
Yes	54 (17.6%)
Non-atopic eczema	12 (3.9%)
Acne	8 (2.6%)
Psoriasis	7 (2.3%)
Atopic eczema	5 (1.6%)
Verruca vulgaris	4 (1.3%)
Rosacea	3 (1.0%)
Dermatomycosis	2 (0.7%)
Urticaria	2 (0.7%)
Other (one respondent per each condition)**	18 (5.8%)

* combinations may occur

** acanthosis nigricans, actinic keratosis, clavus, condyloma, dyshidrosis, fibroma, herpes labialis, hyperhidrosis, impetigo, keloid, keratosis pilaris, metal allergy, naevi, onycomycosis, photosensitivity, seborrhea capitis, trichoepithelioma, vitiligo

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Table 15 Time trade-off utilities for the health states defined by DLQI

Health state	DLQI total score	N	Utilities				Comparison of health states (p)**						
			Mean (SD)	Median	utility=0	utility=1	L1	L2	L3	M1	M2	M3	S
Total sample*													
L1	11	124	0.66 (0.31)	0.80	12 (9.7%)	23 (18.5%)	-	0.320	**0.040**	0.683	**0.022**	0.179	**0.003**
L2	11	127	0.64 (0.28)	0.70	9 (7.1%)	13 (10.2%)	-	-	0.150	0.539	**<0.001**	0.511	**0.012**
L3	11	125	0.59 (0.29)	0.60	7 (5.6%)	14 (11.2%)	-	-	-	0.100	**<0.001**	0.407	0.370
M1	6	125	0.64 (0.32)	0.80	15 (12%)	18 (14.4%)	-	-	-	-	**0.006**	0.354	**0.009**
M2	6	130	0.75 (0.27)	0.85	6 (4.6%)	29 (22.3%)	-	-	-	-	-	**<0.001**	**<0.001**
M3	6	126	0.62 (0.30)	0.70	12 (9.5%)	21 (16.7%)	-	-	-	-	-	-	0.094
S	16	125	0.56 (0.29)	0.60	10 (8.0%)	12 (9.6%)	-	-	-	-	-	-	-
Responses of those without any dermatological condition***													
L1	11	97	0.66 (0.31)	0.80	10 (10.3%)	18 (18.6%)	-	0.158	**0.022**	0.807	**0.067**	0.191	**0.004**
L2	11	105	0.62 (0.28)	0.70	8 (7.6%)	9 (8.6%)	-	-	0.215	0.217	**<0.001**	0.993	0.060
L3	11	105	0.58 (0.30)	0.60	6 (5.7%)	11 (10.5%)	-	-	-	**0.038**	**<0.001**	0.201	0.586
M1	6	108	0.65 (0.32)	0.80	14 (13.0%)	15 (13.9%)	-	-	-	-	**0.033**	0.288	**0.006**
M2	6	101	0.74 (0.27)	0.80	6 (5.9%)	20 (19.8%)	-	-	-	-	-	**0.001**	**<0.001**
M3	6	107	0.62 (0.30)	0.70	10 (9.3%)	16 (15.0%)	-	-	-	-	-	-	0.079
S	16	100	0.55 (0.30)	0.60	9 (9.0%)	10 (10.0%)	-	-	-	-	-	-	-

* Each respondent assessed three different DLQI-defined health states in a randomised order. The total number of TTO responses was 882.

**A Mann-Whitney U test p<0.05 was considered significant (in bold).

*** The total number of TTO responses from participants without any dermatological condition was 723.

In the names of health states, L refers to large impact on HRQoL, M refers to moderate impact on HRQoL and S stands for the most severe health state.

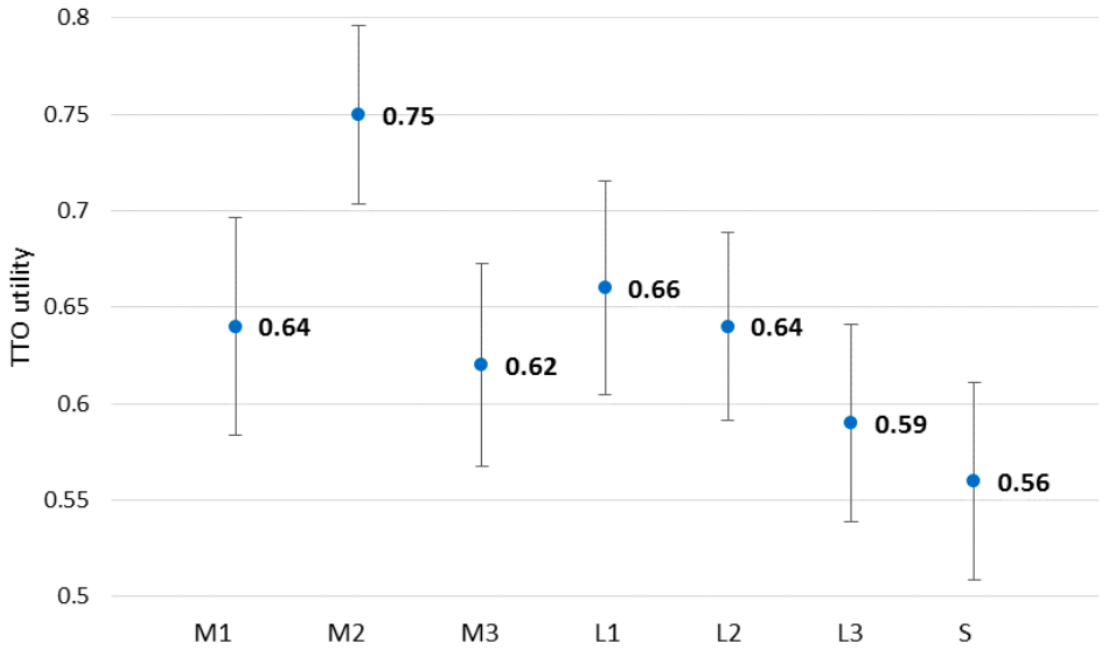

Figure 14 Utility values for the seven health states (mean, 95% CI)

'M1-3' refers to a DLQI total score of 6, 'L1-3' to 11 and 'S' to 16. TTO=time trade-off

4.3.3 Comparison of the utilities

Overall, 21 pairwise comparisons were made between utilities attached to the seven health states: six and 15 between health states of identical and different DLQI total scores, respectively. In three cases out of the six comparisons (50%) significant differences were observed between utilities for health states with identical total DLQI scores. Regarding the 11-point health states (L1-L3), a significant difference was revealed between 'L1' and 'L3'. There was no significant difference between 'L1' and 'L2' or between 'L2' and 'L3' (*Table 15*). Among the three six-point moderate health states, significant differences were found between 'M1' and 'M2', and 'M2' and 'M3', but not between 'M1' and 'M3'. The lack of significant difference was noticed in eight out of the 15 comparisons (53%), where health states for which the DLQI total score differed greater than for the MCID were compared. We found no statistically significant difference between 'S' and 'M3' despite the 10-point difference between these two health states.

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4.3.4 Impact of any dermatological condition on utilities

The mean utilities elicited from respondents who had no dermatological condition were higher than from those who had no skin problem (0.68±0.30 vs. 0.63±0.29, p=0.029). No difference was observed in mean utilities for binocular blindness between these two groups (0.49±0.30 vs. 0.50±0.27, p=0.796). For the single health states, the number of respondents with dermatological illnesses (n=18-28) was too small to detect a significant within-group difference except for health state ‘L2’ (0.75±0.26 vs. 0.62±0.28, p=0.036).

In a sensitivity analysis, after eliminating the responses of participants with any dermatological conditions, only minor changes occurred in mean utilities and in the significance of the differences between health states (*Table 15*).

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5 Discussion

5.1 Psoriasis study

In the 'Psoriasis study', we assessed health status, disease severity and HRQoL in a consecutive sample of 200 moderate-to-severe psoriasis patients from two Hungarian university clinics. As more than half of our patients were treated by systemic biological therapy, our sample represented approximately 8% of the total number of psoriasis patients received biological therapy in Hungary at the time of the survey [148].

5.1.1 Health status and HRQoL in Hungarian moderate-to-severe psoriasis patients

We found notably impaired HRQoL in most EQ-5D dimensions, whilst in addition the EQ-5D index scores compared to the gender- and age-matched general population norms (*Figure 7* and *Figure 8*). However, patients treated by biologicals experienced significantly improved HRQoL. Their mean EQ-5D index score approximated that of the general population of the same age (0.75 vs. 0.81), which is consistent with findings from large RCTs which proved that biological therapy can considerably improve not only clinical outcomes, but also HRQoL [149-151]. Our study therefore provided a clear picture of the burden of living with moderate-to-severe psoriasis, as well as the benefits of biological therapy.

Mean EQ-5D index scores of female patients were significantly lower compared to their male counterparts despite their similar mean PASI scores (*Table 6*). No such difference was revealed in the EQ VAS or DLQI scores; however, this could be a result of the small number of females in the sample. Some prior studies found the same association between gender and HRQoL in psoriasis, using DLQI and Skindex-29 [199, 200], whereas other authors reported that psoriasis affects both sexes equally [127].

The patients' age negatively correlated with their actual EQ-5D scores. However, deviations away from this trend can be found in *Figure 8*. Male psoriasis patients' HRQoL was lower at age 18-24 than at 25-34, or at age 55-64 than at age 65-74. Presumably, older age is associated with improved coping mechanisms and decreased social rejection,

and additionally patients learn how to live with psoriasis and recalibrate their self-assessment of disability over time and report better HRQoL [201, 202].

Fifty-seven patients with moderate-to-severe psoriasis associated with psoriatic arthritis had a substantially reduced HRQoL. Most earlier studies that reported HRQoL in psoriasis associated with psoriatic arthritis enrolled psoriasis patients reporting any severity [200, 203, 204]. Neither of these studies applied the EQ-5D questionnaire. However, in this group of patients, the efficacy of systemic treatments is particularly important to be assessed together, as the real health gain (e.g. expressed in EQ-5D score) might exceed that measured in psoriasis or psoriatic arthritis separately.

The EQ-5D questionnaire was employed in two earlier Hungarian studies enrolling patients with skin diseases [121, 122]. Brodszky et al. assessed HRQoL in 183 psoriatic arthritis patients with a mean age of 50 years and a mean PASI score of 6.5 [121]. The results of our moderate-to-severe psoriasis patients with psoriatic arthritis correspond to their EQ-5D and EQ VAS findings (*Figure 15*).

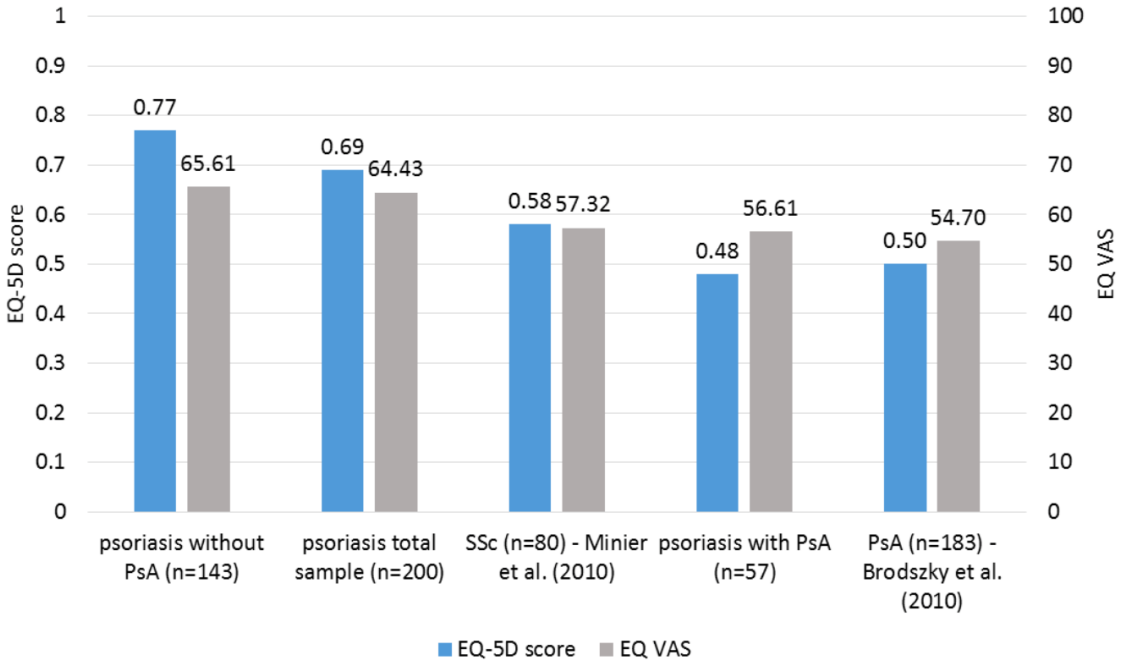

Figure 15 Comparison of EQ-5D and EQ VAS scores in moderate-to-severe psoriasis, psoriatic arthritis and systemic sclerosis in Hungary

PsA = psoriatic arthritis; SSc = systemic sclerosis.
Data sources: Brodszky et al. 2010 [121], Minier et al. 2010 [122]

Minier et al. studied 80 systemic sclerosis (SSc) patients (mean age: 57 years), 60 and 20 of whom had diffuse and limited SSc, respectively [122]. Hungarian SSc patients rated their health worse than psoriasis patients without psoriatic arthritis but better than those with psoriatic arthritis, as measured by either EQ-5D or EQ VAS.

5.1.2 Psoriasis patients' expectations regarding length of life and future HRQoL

Besides the current health state of patients, we assessed their expectations on subjective LE and HRQoL for six months ahead and for future ages.

Notwithstanding the more than 20-year-long disease duration on average, our patients were fairly positive in the short term. They expected an improvement ranging from 0.08 to 0.26 in their EQ-5D score. In most patients, this achieved the MCID for EQ-5D (0.10 and 0.20 for those patients who fulfilled the criteria of PASI25-49 and PASI50-74, respectively) [205]. A possible reason for their optimistic behaviour is that a high proportion of the patients had received biologicals or were about to start their first biological drug (56% and 8% of the 167 patients). The introduction of biologicals to the treatment of psoriasis has considerably changed the expectations and outcomes of patients [206]. The 14 patients at the initiation of their first biological expected on average 0.18±0.27, which seems quite realistic in the light of the results of the RCTs, in which 0.12 to 0.21 improvement in EQ-5D was achieved within 12 to 54 [149, 151, 207, 208]. This is supported by recent registry-based real-life data on 267 Swedish patients initiating their first biological treatment, who improved 0.12±0.24 in their EQ-5D score across various follow-up durations (12-52 weeks) [209]. Moreover, in our sample, expectations of patients about to start their first biological therapy were in line with the actual EQ-5D of patients on biologicals at the time of the survey (0.77 vs. 0.76).

Only female patients from our study expected to live less time than their statistical life expectancy. Multiple comorbidities, particularly the higher risk of cardiovascular diseases, may contribute to decreased life expectancy in psoriasis patients. A large population-based cohort study conducted before the era of biologicals described that male and female patients with severe psoriasis died 3.5 and 4.4 years younger, respectively, than those who lived without psoriasis [210]. Recently, however, systemic treatment

(either biologicals or methotrexate) has been proven to prevent against cardiovascular disease events [211].

Patients expected a great decline in their HRQoL for the future ages of 60 to 90, respectively. This is notably lower than results for the age-matched participants of a similar study among the Hungarian general population (*Figure 9*) [165]. Nonetheless, expectations in the long run might be biased by age norms and might not reflect on changes of age norms and longevity that have happened in the last 20 years [212]. Thus, it can be assumed that patients' poor expectations are not self-fulfilling prophecies.

Earlier, a similar study was carried out involving Hungarian rheumatoid arthritis patients on the initiation of their first biological drug (n=92, mean age: 51.1±11.9) [166]. They expected a 0.39 improvement in their EQ-5D scores within three months compared to the average 0.18 improvement within six months expected by psoriasis patients (n=14). Yet, very similar expectations can be observed for each future decade with the exception of the age of 90, where psoriasis patients expected significantly lower EQ-5D scores.

5.1.3 Recommendations for future research

In future studies, it would be useful to assess the HRQoL of mild psoriasis patients also from Hungary. Other preference-based measures, such as the TTO, are suggested to be employed in this regard. More attention should also be paid to measuring HRQoL in less prevalent types of psoriasis (e.g. guttate, inverse and palmoplantar psoriasis), and it would be very beneficial to investigate the expectations of younger and newly diagnosed patients' expectations across different time frames. We strongly encourage researchers to explore whether the relationship between future expectations and long-term prognosis exists, and whether it influences the findings of clinical trials of new interventions.

5.1.4 Limitations

Some limitations need to be considered. First, patients were recruited from two university clinics in the two largest cities of Hungary, and about half of them were treated by biological drugs. No information is available on the health status of untreated patients or whether patients treated in other centres are different from these patients. Thus, the

external validity of the results may be limited, and our findings may not be generalisable to all moderate-to-severe psoriasis patients in Hungary. Secondly, the Hungarian statistical LE data used for the comparisons were gender- and age-matched, but other socioeconomic determinants, such as the level of education, marital status and monthly income, were not adjusted.

5.2 Pemphigus study

The 'Pemphigus study' consisted of two large parts, namely a systematic review and a meta-analysis of the existing literature on HRQoL studies in pemphigus and a valuation of utilities for pemphigus health states from the general population.

5.2.1 Systematic review and meta-analysis

We performed the first systematic literature review and meta-analysis of HRQoL studies in pemphigus. Overall, 16 original papers from eight different countries on five continents were found that had assessed HRQoL in 1,456 patients with pemphigus. Two earlier reviews dealt with the HRQoL of pemphigus patients, but neither of them applied a systematic search strategy or a meta-analysis [213, 214]. In all studies, a great negative impact of pemphigus on HRQoL was observed. Compared to healthy controls or the general population, significantly lower HRQoL was reported in most dimensions of SF-36 [184, 191, 194, 196, 198].

The meta-analysis indicated a higher mean DLQI score (12.0) than previously reported in psoriasis (10.5) or atopic dermatitis (11.2) [3]. Three out of the 16 studies compared HRQoL of pemphigus and psoriasis patients, and each reported a similar or a significantly lower level of HRQoL in pemphigus than that in psoriasis, particularly in the PF, RP and GH domains [186, 191, 194]. Moreover, a recent study described that compared to other chronic aphtous diseases (e.g. oral lichen planus, recurrent aphthous ulcers), pemphigus patients had the worst HRQoL assessed with COMDQ [215]. These findings highlight the severe health loss caused by pemphigus, which might even exceed that experienced in other severe chronic dermatological conditions.

In line with other studies, remarkably high, overall 28% to 78% of patients were found GHQ-positive (i.e. GHQ-12≥4 or GHQ-28≥6), thereby indicating a probable non-

psychotic psychiatric comorbidity, such as anxiety or depression [216-218]. The psychological vulnerability of patients is important to consider when selecting a treatment, as currently systemic corticosteroid therapy represents a first-line treatment for pemphigus, which may induce various psychiatric disorders [46]. Moreover, depression and side-effects or corticosteroids may cause suicidal ideations or behaviour in patients [219].

Along with psychological impairment, higher disease severity was the most important determinant of decreased HRQoL in pemphigus. However, only PGA and the Ikeda-index have been administered in these studies, which are not considered as objective and validated severity scoring systems for pemphigus [42, 45]. Consequently, in further HRQoL studies, the Pemphigus Disease Area Index (PDAI) or the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) are recommended to be used [43, 44, 220, 221]. The impact of several other factors on HRQoL, such as age, sex, type of pemphigus, disease duration, mucocutaneous involvement, clinical activity, itching, skin burning or being treated by adjuvant drugs, cannot be stated clearly and should be investigated further.

5.2.2 Valuation of pemphigus health states by the general population

As our systematic review illustrated, no study in the literature has reported health state utility values for pemphigus. Thus, we carried out a questionnaire-based survey, using a preference-based outcome measure to provide health utilities for pemphigus. We elicited utilities from 108 participants of the general population, using VAS and TTO.

We found that utilities for PV were significantly worse compared to PFo, which is in accordance with the results provided by Paradisi et al., which compared the HRQoL of patients with these two forms of pemphigus by Skindex-29 [191]. However, the number of PF patients in their study was very low (n=10).

Despite the negative utilities allowed in our TTO task, corresponding VAS scores were significantly lower (0.25, 0.38 and 0.64). This is comparable to results of a German study in a sample of predominantly PV patients [222]. The authors reported that after 11 months of rituximab therapy, patients' mean VAS score (assessed by their physicians)

improved from a mean 34 to 75 [222]. It is well-known from the literature that VAS typically leads to lower utilities than TTO [94]. Several explanations address this difference (e.g. in the VAS task participants do not consider the duration of the health state, or many people tend to interpret VAS as a percentage of a functioning scale or the absence of opportunity cost within the VAS), all of which may support the lower VAS scores [92].

The utility associated with uncontrolled pemphigus was found to be worse than in uncontrolled atopic dermatitis (0.64) or psoriasis (0.56), similar to severe scleroderma (0.37) but better than severe psoriatic arthritis (0.29) assessed by the general public [100, 223]. Nevertheless, a comparison of these findings is problematic, because methodological variations across studies may exist. For example, the time frame was set at 10 years in the current study, whereas participants could trade from their full life expectancy in others. Another factor that may hamper such comparisons is that we allowed the respondents to consider health states to be worse than dead, and hence utilities ranged between -1 and 1. Other authors, on the contrary, did not rate negative values.

5.2.3 Recommendations for future research

Very limited literature is available on HRQoL in clinical forms other than PV, and so few participants in a study makes it very difficult to detect statistically significant and also clinically meaningful differences amongst subgroups characterised by different clinical features. In order to improve the awareness about HRQoL impairment related to pemphigus, studies including larger patient numbers, preferably multicentre and/or multinational, are suggested.

The use of newly developed disease-specific HRQoL tools, namely the Autoimmune Bullous Disease Quality of Life (ABQOL) and the Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) are recommended [172, 224]. These questionnaires proved validity and reliability, and they are very promising for serving as endpoints in clinical trials of pemphigus [221]. Furthermore, as pemphigus is a life-long disease with flare-ups followed by quiescent periods, longitudinal studies would help to explore its disease course in terms of HRQoL.

Our utility values were elicited from the general public, so they reflect social preferences. These general population values are typically recommended to be used in cost-effectiveness analyses, in order to support reimbursement decision-making on health interventions [89-91], nonetheless, discrepancies may occur between utilities derived from patients and members of the general public (see in details in *Chapter 1.3.2*). Future studies assessing utilities in pemphigus patients with various types and severity are recommended.

5.2.4 Limitations

Our systematic review has some limitations. First, the various HRQoL instruments applied, the different sample sizes and the geographic locations make the comparison of these 16 studies less certain. Therefore, the role of most factors affecting the HRQoL of pemphigus patients is still unclear. Second, in most cases, HRQoL tools were not applied by a sufficient number of studies to conduct a meta-analysis. Third, substantial heterogeneity was detected across both the SF-36 and Skindex-29 studies, a proportion of which most likely stems from variations in the study populations in terms of age, disease duration, sex ratio, clinical type and disease severity. Many studies, however, failed to report such data. For instance, the type of pemphigus was unknown or not specified in 22% of the patients.

The utility assessment in pemphigus has limitations, too. First, a convenience sample was recruited to the study which was not representative of the Hungarian population. However, we found that age, gender and employment status were not reliably associated with TTO answers. A higher level of education was related to higher TTO utilities. Second, the smallest tradable amount of time was six months. As the rate of ‘1’ answers for the controlled pemphigus health state was as high as 26%, the respondents might have given up time if smaller units of time, such as a few weeks or even days, had been offered. Finally, there were a few inconsistent answers, which may be the consequence of the self-completion method (*Appendix 12.4*). The results, nevertheless, did not change after the elimination of these answers (*Table 13*).

5.3 DLQI study

In this study, we measured utility values using time trade-off method for seven selected health states described by the 10 items of the DLQI. We found that health states with identical total DLQI scores may be valued as significantly different in their utility scores, whereas those that differed more than the MCID may have received equal utilities (*Table 15*). These findings have many theoretical implications regarding the use of DLQI as a benchmark in clinical and financial decisions.

5.3.1 Theoretical implications

As described in detail in *Chapter 1.3.2.4* and *Chapter 1.3.3*, the DLQI currently plays the most important role in the management of psoriasis patients. The European-S3 Guidelines recommend biological therapy to moderate-to-severe psoriasis patients who meet (BSA > 10 or PASI > 10) and DLQI > 10 [28, 29]. To be eligible for maintenance biological treatment, patients need to demonstrate an at least five-point improvement in their DLQI scores for weeks 10 to 16 [28]. Furthermore, in many European countries, reimbursement guidelines for biological therapy also involve the DLQI (*Table 1*). In the following, based on these guidelines, three examples are given to illustrate the possible consequences of the discrepancies observed between DLQI scores and utilities.

Example 1

Let us suppose two patients with moderate-to-severe psoriasis – one of them is in health state ‘M1’, while the other is in ‘L2’ (*Table 4*). The first patient has a DLQI total score of 6, while the second has 11. Their HRQoL expressed in utilities, however, is equal (0.64) (*Figure 14*). Assuming they have a similar severity score (PASI >10), only the first patient is entitled to receive biological therapy according to the guidelines, in spite of the fact that their utility scores are identical.

Example 2

Let us assume a patient with moderate-to-severe psoriasis who is in health state ‘S’ (DLQI=16) and fulfils the severity scores to be eligible for biological treatment. The patient commences biological therapy and as a result of the treatment moves to health

state ‘M3’. Thus, the DLQI score for this patient is reduced by 10 points, which exceeds twice the MCID. In utilities, however, this improvement yields a mere increase of 0.06 (p=0.094) (*Table 15*), implicating that a clinically meaningful improvement in DLQI is not necessarily accompanied by significant health gains.

Example 3

Let us suppose two moderate-to-severe psoriasis patients with a DLQI total score of 11. The first patient is in health state ‘L1’, the other is in ‘L3’ (*Table 4*). The utility score of the first patient is significantly higher (0.66 vs. 0.59, p=0.040) (*Table 15*). This finding has two important implications. First, as ‘L1’ and ‘L3’ only differ in the number of negatively affected items and/or the levels of impairment, our results suggest that DLQI items might not be weighted equally. This is supported by earlier studies that argued for the uni-dimensionality of the DLQI based on findings from Rasch-analyses in psoriasis, atopic dermatitis and neurodermatitis [131-133, 135, 136]. Secondly, if they meet PASI>10, biological therapy is recommended for both patients (‘L1’ and ‘L3’). However, considering the fact that there is a significant difference between their pre-treatment utility values, we assume that the average utility gain achieved with biological therapy, as well as cost-effectiveness, will vary between these two patients.

5.3.2 Recommendations for future research

In future studies, a larger number of DLQI health states is recommended to be elicited, preferably from a representative sample of the general population. This would allow one to develop a mapping model that could predict utilities for DLQI health states. As we found differences between utilities assessed by those with and without any dermatological condition, a repeat of this experiment in selected patient populations, especially in psoriasis, atopic dermatitis, urticaria, acne and vitiligo, in which the DLQI is most commonly used [3], or in a mixed sample of chronic dermatological patients, is suggested. This could confirm our findings, as well as identify the preferences of the patients. If similar discrepancies were justified between the DLQI scores and utilities derived from various patient populations, this would help the development of clinical and financial guidelines in dermatology.

5.3.3 Limitations

This study has a number of limitations to consider. First, DLQI is a dermatology-specific instrument, and it is assumed to be more sensitive to small but clinically relevant changes in HRQoL than the TTO. This may explain in part that utilities for health states that differed more than the MCID were not statistically significantly different from each other. Secondly, due to the Internet experiment, there was a slight overrepresentation of participants with dermatological conditions, as usually people tend to be more interested in a survey related to their own illness. But, in a sensitivity analysis, only minor changes were observed after excluding these respondents (*Table 15*). Finally, respondents may have considered the description of some health states quite unrealistic and found it difficult to imagine, because of the lack of information on the extent of skin lesions, involved body parts, appearance of the skin or the type or name of any particular skin disease. Nevertheless, adding this information might have biased the results, because these aspects are not covered by the 10 items of the DLQI.

5.4 Implications for decision-making in healthcare

The three studies in this thesis are united by a common focus on HRQoL and health utilities in healthcare decisions made in the field of dermatology. In the past 20 years, there have been a number of major advances in the treatment of chronic skin diseases, of which biological drugs represent the most prominent example. These treatments, nevertheless, account for high costs; for example, in Hungary, the mean annual drug costs attributed to moderate-to-severe psoriasis patients receiving biological therapy were 4.01 million HUF (€14,084) [3] per patient (2014) [162]. Most societies cannot afford to treat all patients regardless of the severity of their disease, and so they have to make a decision about who to treat or who not to treat. The decision, however, is very complex and involves a series of outcomes, including HRQoL.

For physicians as well as payers, clear cut-off points on HRQoL measures need to be implemented to support clinical and financial decisions about treatments. A DLQI score of 10 is often considered such a cut-off value in the management of many chronic

[3] EUR 1 = HUF 285 (year 2014)

skin conditions, such as moderate-to-severe psoriasis. However, the discrepancies found between DLQI scores and TTO utilities in our 'DLQI study' raise many concerns regarding the appropriateness of using DLQI in such judgements (see in detail: *Chapter 5.3.1*). The incorporation of the DLQI into clinical and financial guidelines on the treatment of moderate-to-severe psoriasis has undoubtedly been a large step towards more effective patient management, because it reflects patients' perspectives. Nevertheless, if the tool is not accurate enough, it can still lead to biases in decision-making, which may in turn distort the allocation of healthcare resources. Many European countries that currently apply the DLQI in their clinical and/or financial guidelines, such as the UK, Denmark, Sweden, Hungary and Poland, may be implicated (see more examples in *Table 1*). Thus, based on our findings, the use of the DLQI in clinical and financial decision-making can be called into question and needs to be investigated further.

Overall, in this thesis, a number of distinct utility values were presented for pemphigus and moderate-to-severe psoriasis. The low utilities found in these conditions, especially in certain clinical subtypes such as pemphigus vulgaris, palmoplantar psoriasis and psoriatic arthritis, highlight that severe chronic dermatological diseases may cause serious health loss. These findings may have implications for priority setting in health policy.

The HRQoL and utility results from this thesis may help to shape the picture in the minds of healthcare policymakers regarding what they think about the burden of chronic skin diseases. We found that the effective treatment of psoriasis and pemphigus might result in considerable health gains which may, however, stem from a multitude of outcomes – only a fraction of which can be captured by disease-severity measures alone. By measuring utility values that incorporate many other dimensions of HRQoL, such as work capacity, daily activities, relationships, leisure time and mental health, among others, greater health gains can be achieved. For instance, psoriasis patients who received no systemic therapy, traditional systemic therapy or biological therapy reported mean EQ-5Ds of 0.65, 0.62 and 0.75, respectively. Corresponding mean annual costs of these patients were 0.62 million, 0.68 million and 4.5 million HUF (€2186, €2388, €15,790)[4] [162]. The large differences in utilities between psoriasis patients within these treatment

[4] EUR 1 = HUF 285 (year 2014)

groups, or between the uncontrolled and controlled pemphigus health states, provide evidence on the value for money achieved through very costly treatments.

Both the EQ-5D results in psoriasis and the TTO utilities in pemphigus may serve as a basis for formal economic evaluations of health interventions. In many countries, including Hungary, new treatments are required to demonstrate cost-effectiveness for drug reimbursement decisions. For cost-effectiveness analyses, the HTA guidelines of many countries, again including Hungary, prioritise the use of country-specific HRQoL data assessed by preference-based measures, particularly the EQ-5D [9, 89-91]. Until our studies, locally-relevant utility data were not available either in psoriasis or pemphigus. Following two previous studies on rheumatoid arthritis and chronic migraine, we were the first to provide TTO utilities for a dermatological condition [225, 226].

Before our study, there were no utility scores available from Hungary in the field of dermatology. Thus, results transferred from other jurisdictions were used for cost-effectiveness models and decision-making regarding the management of these patients. Nonetheless, the actual health statuses and utility values of patients in other countries may be different from those in Hungary. Variations perceived in epidemiology, severity of the disease, practice guidelines and many other factors suggest the existence of differences between countries. Transferring utilities may lead to inaccurate conclusions [227]. Utility values from the studies in this thesis are therefore very useful in developing more accurate cost-utility models, and eventually for patients to receive treatment covered by health insurance. Given the similarities in health systems, the EQ-5D scores in psoriasis can be used in other CEE countries until country-specific EQ-5D data are obtained. As we were the first to elicit utility values for pemphigus health states in the literature, our utility scores may be used in economic evaluations in other countries as well.

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6 Conclusions

This thesis aimed to investigate HRQoL and utility values in chronic skin diseases in Hungary. To accomplish this goal, three original studies – two disease-specific investigations and a study examining the relationship between DLQI and utility scores – were carried out in Hungary between 2012 and 2015 [10-16].

6.1 Psoriasis study

Based on our findings, the following conclusions can be drawn:

1. This is the first study from Hungary specifically, and more broadly from the whole Central and Eastern Europe, that has used the EQ-5D questionnaire in psoriasis patients. For most age groups, the health status and general HRQoL of moderate-to-severe psoriasis patients is significantly deteriorated compared to the gender- and age-matched EQ-5D population norm in Hungary. Palmoplantar psoriasis and psoriatic arthritis are associated with the largest impairment in HRQoL. Patients receiving biological therapy demonstrate better HRQoL compared with those on any other treatment.
2. Male patients expect a longer life, while females expect a shorter life compared to their statistical life expectancy. Patients' short-term expectations regarding their HRQoL are mainly positive, while a great decline is expected for future ages. Expectations are influenced by age, gender, clinical subtype, disease severity, current HRQoL and applied therapy. Our findings illuminate a new dimension of the lifelong burden experienced by psoriasis patients.

6.2 Pemphigus study

6.2.1 Systematic review and meta-analysis

We provided a comprehensive overview of the current scientific knowledge about HRQoL in pemphigus patients. The study pointed out the following:

1. Pemphigus patients suffer the most problems in the role-physical dimension of HRQoL, followed by role-emotional and vitality.
2. Overall, 41 possible determinants of HRQoL were identified, amongst which clinical severity and associated psychological impairment were revealed as the most important.
3. There is a need for longitudinal studies in order to explore the disease course of pemphigus with regard to HRQoL.
4. No preference-based HRQoL instruments have yet been applied in pemphigus; thus, input data are missing to calculate QALYs in cost-effectiveness analyses of treatments.

6.2.2 Valuation of pemphigus health states by the general population

The main conclusions of the study are as follows:

1. This study provides the first utility values for pemphigus health states. Our utilities may serve as a guide for further utility studies and cost-effectiveness analyses.
2. Pemphigus vulgaris is associated with significantly lower utility values than pemphigus foliaceus.
3. The successful treatment of pemphigus might result in large utility gains, which is very promising for future cost-effectiveness studies involving various treatments for pemphigus patients.

6.3 DLQI study

Given the discrepancies found between DLQI scores and utilities:

1. HRQoL may differ a great deal between patients whose DLQI total scores are identical.
2. Patients with DLQI scores differing more than the MCID may have identical HRQoL expressed in their utilities.
3. A reduction in the DLQI score may not be associated with significant (or any) health gains.

As a consequence, the DLQI may distort clinical and financial decisions made during the management of chronic skin diseases.

6.4 General conclusions with policy implications

This thesis provides important information for clinical decision-making, as well as for financing and policymaking in healthcare. First, our results have uncovered concerns about the most commonly used HRQoL measure in dermatology, the DLQI. In the light of our findings, the use of DLQI for everyday clinical practice may distort many clinical decisions made on a daily basis by physicians, such as judging severity or treatment effects, hospital admission decisions or treatment selection. Considering the number of illnesses in which the DLQI is used, the amount of patients affected worldwide may be very large. Furthermore, in certain diagnoses, such as moderate-to-severe psoriasis or chronic hand eczema, the DLQI is used to support reimbursement decisions about treatments. These decisions might well be biased and thereby compromise the cost-effective management of chronic skin diseases and the efficiency of healthcare systems. This implicates many European countries where financial guidelines on the management of chronic skin diseases involve the DLQI.

Second, our utility values for pemphigus and psoriasis demonstrate evidence on the large health losses experienced by patients with chronic skin diseases. Results on psoriasis patients' short-term expectations about their HRQoL have a practical usefulness for the management of dermatological patients. In clinical settings, careful consideration of overoptimistic expectations regarding the impact of treatments on HRQoL may help to avoid healthcare provider disappointment. Conversely, handling pessimistic expectations can contribute to an improvement in clinical outcomes. Exploring expectations is a way to strengthen the physician-patient relationship.

Finally, utility estimations from our studies have policy implications. In many countries, including Hungary, cost-effectiveness evidence is required for reimbursement decisions concerning health interventions. The utility values provided for the pemphigus and psoriasis health states in this thesis are key input parameters for cost-effectiveness models. The accurate measurement of utilities is crucial, because it greatly influences cost-effectiveness estimations, and thus financing decisions about treatments. Our results are among the first utility values for dermatological conditions in Hungary, and they

represent the basis of local data-driven HTA and healthcare decision-making about chronic skin diseases. The availability of country-specific utilities allows one to generate health system-specific cost-effectiveness estimates. The growth of such locally-relevant data improves the quality of cost-effectiveness analyses and eventually health system efficiency.

We hope that these results from the three empirical investigations in this thesis will foster more research in the field, as well as promote discussions and debates about the use of HRQoL data for clinical and financial decision-making in dermatology.

6.5 New findings of the thesis

This thesis represents the first thorough investigation of HRQoL and utilities in chronic skin diseases in Hungary. Beyond national importance, the three studies contribute new knowledge about HRQoL in dermatology.

Importance on the international level

1. The discrepancies identified between DLQI scores and utility values question the use of the DLQI in clinical and financial decision-making.
2. We were the first to explore psoriasis patients' expectations regarding their life expectancy and future HRQoL. We explored a number of socio-demographic and clinical features influencing the under- and overestimating behaviour.
3. We conducted the first systematic review summarising HRQoL findings in pemphigus. We performed meta-analyses on SF-36, DLQI and Skindex-29 outcomes. Moreover, a total of 41 socio-demographic, clinical, treatment-related and psychological determinants of HRQoL were identified.
4. We assessed utility values for pemphigus health states for the first time in the literature. Our utilities for uncontrolled pemphigus vulgaris, foliaceus and controlled pemphigus can be used as a basis of future cost-effectiveness analyses of pemphigus treatments.

Importance for Hungary

1. Our study was the first to examine the health status and HRQoL of moderate-to-severe Hungarian psoriasis patients, using the EQ-5D health survey. For most age groups, we found significantly lower EQ-5D index scores in moderate-to-severe psoriasis patients compared to the general population. Following psoriatic arthritis and scleroderma, psoriasis is the third dermatological condition for which EQ-5D utilities have been evaluated in Hungary.
2. We provided the first data on HRQoL benefits of biological therapies for moderate-to-severe psoriasis at the national level.
3. Our studies resulted in the first local utility values in psoriasis (EQ-5D) and pemphigus (TTO) in Hungary. After rheumatoid arthritis and chronic migraine, pemphigus is the third disease for which country-specific TTO utilities are available.

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7 Summary

This thesis aimed to investigate the effect of chronic skin diseases on health-related quality of life (HRQoL) and utility values, with a special focus on issues influencing clinical and financial decision-making in healthcare. The core of the work is formed by three independent, empirical researches carried out between 2012 and 2015 in Hungary.

We were the first to assess the health status of psoriasis patients, using the EQ-5D for Hungary specifically, and in a broader sense for the whole of Central and Eastern Europe. Moreover. This was the first study to explore expectations regarding patients' life expectancy and HRQoL for six months ahead and future ages of 60-90. Significant deteriorations in HRQoL were noted in most of the 200 moderate-to-severe psoriasis patients compared to the gender- and age-matched general population. In the short term, patients were very optimistic regarding their health state, whereas large-scale deterioration was expected for each future decade. Expectations were influenced by age, gender, clinical subtype, disease severity, current HRQoL impairment or applied therapy.

As a part of the second study, a systematic review of the existing literature and a meta-analysis of studies with Short form-36, Skindex-29 and Dermatology Life Quality Index (DLQI) outcomes in pemphigus were performed. Then, we evaluated utility values through visual analogue scale and time trade-off (TTO) methodologies for three pemphigus health states in a general population sample. This was the first study in the literature to elicit utilities for pemphigus vulgaris and foliaceus. Our utility values can be used as a guide for future utility studies and cost-effectiveness analyses.

In the third investigation, we estimated utilities, using TTO for seven different health states described by the DLQI for members of the general public. We found significant differences between the health states of identical DLQI total scores (in three out of the six comparisons) and the absence of significant differences between health states differed more than the minimal clinically important difference (in eight out of the 15 comparisons). The discrepancies found between DLQI scores and utilities raise many concerns regarding the appropriateness of using DLQI for clinical and financial decisions.

The three studies collectively provide new evidence to inform clinicians as well as healthcare policymakers about the true burden of chronic skin diseases and the value for money being achieved through public expenditure. The main findings evoke many questions and call for further research to elaborate the role of HRQoL assessment in clinical and financial decision-making in the field of dermatology.

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8 Összefoglalás

Értekezésem a krónikus bőrgyógyászati betegségek okozta életminőség-csökkenés és hasznosság-vesztesség vizsgálatát tűzte ki célul, különös tekintettel az orvos-szakmai és finanszírozói döntéseket befolyásoló területekre. A disszertáció három önálló, empirikus kutatáson alapul, melyeket 2012 és 2015 között végeztünk.

Magyarországon és Közép-Kelet Európában is elsőként vizsgáltuk psoriasisos betegek egészségi állapotát és életminőségét az EQ-5D kérdőívvel. Nemzetközi szinten is elsőként mértük fel a betegek élettartammal és életminőséggel kapcsolatos várakozásait egy rövidebb 6 hónapos időtávon, illetve évtizedenként 60-90 éves korukra. Kimutattuk, hogy a kutatásba bevont 200 középsúlyos vagy súlyos psoriasisos beteg többségének egészségi állapota szignifikánsan rosszabb a hazai – nemben és életkorban illesztett – általános populációhoz képest. A betegek rövid távon inkább javulást vártak egészségi állapotukban, ezzel szemben idősebb korukra fokozatos mértékű, igen jelentős rosszabbodást. A várakozásokat befolyásolta az életkor, nem, psoriasis típusa, betegségsúlyosság, aktuális életminőség és az alkalmazott terápia.

Második kutatásunk részeként szisztematikus irodalomkeresést végeztünk pemphigusos betegek életminőségével kapcsolatos tanulmányokra vonatkozóan, továbbá metaanalízissel elemeztük az SF-36, Skindex-29 és Bőrgyógyászati Életminőség Index (DLQI) eredményeket. Ezután meghatároztuk három, pemphigusszal összefüggő egészségi állapot hasznosságát vizuális analóg skála és időalku módszerekkel általános populációs mintán. A szakirodalomban elsőként közöltünk hasznosságértékeket pemphigus vulgarisban és foliaceusban, melyek későbbi egészség-gazdaságtani elemzéseknek szolgálhatnak alapjául.

A harmadik kutatásban hét különböző, a DLQI kérdőív tíz elemével leírt egészségi állapot hasznosságát vizsgáltuk időalku módszerrel, általános populációs mintán. Az azonos DLQI összpontszámú állapotok hasznosságértékei hatból három esetben szignifikánsan különböztek. A minimális klinikailag fontos különbségnél nagyobb DLQI pontszámban eltérő egészségi állapotok hasznossága 15-ből nyolc esetben nem tért el szignifikánsan. A DLQI és a mért hasznosság értékek között talált ellentmondások megkérdőjelezhetik a DLQI alkalmazását klinikai és finanszírozói döntéshozatalban.

Kutatásaink új eredményekkel szolgálnak a krónikus bőrgyógyászati betegségek okozta betegségteherről, valamint hozzájárulhatnak az egészségügyi erőforrások értékalapú felhasználásához. Az eredmények számos új kérdést vetnek fel, és rámutatnak további kutatások szükségességére a bőrgyógyászat területén az életminőség értékek orvos-szakmai és finanszírozói döntéshozatalban való felhasználását illetően.

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10 List of publications

10.1 Publications related to this thesis

Peer-reviewed journal articles

1. **Rencz F**, Baji P, Gulácsi L, Kárpáti S, Péntek M, Poór AK, Brodszky V. (2015) Discrepancies between the Dermatology Life Quality Index and utility scores. Qual Life Res, 2015 Dec 18. [Epub ahead of print]

2. **Rencz F**, Gulácsi L, Tamási B, Kárpáti S, Péntek M, Baji P, Brodszky V. (2015) Health related quality of life and its determinants in pemphigus: a systematic review and meta-analysis. Br J Dermatol, 173: 1076-80.

3. **Rencz F**, Holló P, Kárpáti S, Péntek M, Remenyik E, Szegedi A, Balogh O, Herédi E, Herszényi K, Jókai H, Brodszky V, Gulácsi L. (2015) Moderate to severe psoriasis patients' subjective future expectations regarding health-related quality of life and longevity. J Eur Acad Dermatol Venereol, 29: 1398-405.

4. **Rencz F**, Brodszky V, Péntek M, Balogh O, Remenyik E, Szegedi A, Holló P, Kárpáti S, Jókai H, Herszényi K, Herédi E, Szántó S, Gulácsi L. (2014) Disease burden of psoriasis associated with psoriatic arthritis in Hungary. Orv Hetil, 155: 1913-21.

Published abstracts

5. **Rencz F**, Gulácsi L, Tamási B, Kárpáti S, Brodszky V. (2015) Social Utility Values for Pemphigus Vulgaris and Foliaceus: A Composite Time Trade-Off Study. Value Health, 18: A673. (International Society For Pharmacoeconomics and Outcomes Research 18th Annual European Congress, November 7-11, 2015, Milan, Italy)

6. **Rencz F**, Kárpáti S, Baji P, Péntek M, Gulácsi L, Brodszky V. (2015) Valuation of health states defined by Dermatology Life Quality Index using time trade-off. (P1842). (24th European Academy of Dermatology & Venereology (EADV) Annual congress, October 7-11, 2015, Copenhagen, Denmark)

7. **Rencz F**, Gulácsi L, Remenyik É, Szegedi A, Holló P, Kárpáti S, Péntek M, Brodszky V. (2014) Subjective Expectations Regarding Life Expectancy And Health Related Quality Of Life In Moderate To Severe Psoriasis Patients. Value Health, 17: A611. (International Society For Pharmacoeconomics and Outcomes Research 17th Annual European Congress, November 8-12, 2014, Amsterdam, The Netherlands)

10.2 Publications not related to this thesis

1. Brodszky V, **Rencz F**, Péntek M, Baji P, Lakatos PL, Gulácsi L. (2016) A budget impact model for biosimilar infliximab in Crohn's disease in Bulgaria, the Czech Republic, Hungary, Poland, Romania and Slovakia. Expert Rev Pharmacoecon Outcomes Res, 16: 119-125.

2. Baji P, Gulácsi L, Lovász BD, Golovics PA, Brodszky V, Péntek M, **Rencz F**, Lakatos PL. (2016) Treatment preferences of originator versus biosimilar drugs in Crohn's disease; discrete choice experiment among gastroenterologists. Scand J Gastroenterol, 51: 22-7.

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5. **Rencz F**, Péntek M, Bortlik M, Zagorowicz E, Hlavaty T, Liwczyński A, Diculescu MM, Kupcinskas L, Gecse KB, Gulácsi L, Lakatos PL. (2015) Biological therapy in inflammatory bowel diseases: Access in Central and Eastern Europe. World J Gastroenterol, 21: 1728-1737.

6. **Rencz F**, Brodszky V, Péntek M, Bereczki D, Gulácsi L. (2015) Health state utilities for migraine based on attack frequency: a time trade-off study. Neurol Sci, 36: 197-202.

7. Moradi M*, **Rencz F***, Brodszky V, Moradi A, Balogh O, Gulácsi L. (2015) Health Status and Quality of Life in Patients with Psoriasis: An Iranian Cross-Sectional Survey. Arch Iran Med, 18: 153-159.
   joint first authors

8. Fábián M, Tóth V, Somlai B, Hársing J, Kuroli E, **Rencz F**, Szakonyi J, Tóth B, Kuzmanovszki D, Kárpáti S. (2015) Retrospective analysis of clinicopathological characteristics of pregnancy associated melanoma. Pathol Oncol Res, 21: 1265-71.

9. Baji P, Brodszky V, **Rencz F**, Boncz, I, Gulácsi L, Péntek M. (2015) Health state of the population in Hungary between 2000-2010. Orv Hetil, 156: 2043-2052

10. **Rencz F**., Brodszky, V., Varga, P., Gajdácsi J., Nyirády, P., Gulácsi, L. (2014) The economic burden of prostate cancer: a systematic literature overview of registry-based studies. Orv Hetil, 155: 509-520.

11. Heredi E*, **Rencz F***, Balogh O, Gulacsi L, Herszenyi K, Hollo P, Jokai H, Karpati S, Pentek M, Remenyik E, Szegedi A, Brodszky V. (2014) Exploring the relationship between EQ-5D, DLQI and PASI, and mapping EQ-5D utilities: a cross-sectional study in psoriasis from Hungary. Eur J Health Econ, 15: S111-119.
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12. Gulacsi L, **Rencz F**, Pentek M, Brodszky V, Lopert R, Hever NV, Baji P. (2014) Transferability of results of cost utility analyses for biologicals in inflammatory conditions for Central and Eastern European countries. Eur J Health Econ, 15: S27-34.

13. Gulacsi L, Rotar AM, Niewada M, Loblova O, **Rencz F**, Petrova G, Boncz I, Klazinga NS. (2014) Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria. Eur J Health Econ 15: S13-25.

14. Brodszky V, Péntek M, Baji P, **Rencz F**, Géczi L, Szűcs M, Berczi C, Gulácsi L. (2014) Clinical efficacy and safety of enzalutamide in metastatic castration-resistant prostate cancer: systematic review and meta-analysis Magy Onkol, 58: 189-197.

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To Peep Stalmeier (Radboud University Medical Centre, Nijmegen);

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12 Appendices

12.1 Appendix – Domains and scoring of HRQoL instruments related to this thesis

	HRQoL instrument	No. of items	Domains	Scoring	Recall period	Reference
MAU	EQ-5D-3L	5	1. Mobility 2. Self-care 3. Usual activities 4. Pain/discomfort 5. Anxiety/depression	Each domain has three response levels (no problems, some problems and severe problems). Responses are transformed into a utility score by the scoring algorithm.	1 week	[113, 114]
Generic profile instruments	SF-36	36	1. Physical functioning (PF) 2. Role physical (RP) 3. Bodily pain (BP) 4. General health (GH) 5. Vitality (VT) 6. Social functioning (SF) 7. Role emotional (RE) 8. Mental health (MH)	Each domain is scored on a scale from 0 to 100, where higher scores indicate better health. Scores of domains 1-4 are summarised into a Physical Component Summary (PCS) score, whereas domains 5-8 are summarised into a Mental Component Summary (MCS).	4 weeks	[125, 126]
	WHOQOL-BREF	26	1. Physical health 2. Psychological health 3. Social relationship 4. Environment	The items give a total score of 26-130, where a higher score is indicating a better HRQoL.	2 weeks	[228]
	WHODAS-II	36	1. Cognition 2. Mobility 3. Self-care 4. Getting along 5. Life activities (household and work) 6. Participation	The score for each item ranges from 1-5, and higher scores indicate greater disability. The sum of the scores of the items across all domains constitutes the total score.	30 days	[229]

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	HRQoL instrument	No. of items	Domains	Scoring	Recall period	Reference
Dermatology-specific instruments	Dermatology Life Quality Index (DLQI)	10	1. Symptoms and feelings 2. Daily activities 3. Leisure 4. Work/school 5. Personal relationships 6. Treatment	Each question is scored on a 4-point scale (0-3). The total score, obtained by summing the scores of the 10 items, ranges from 0 to 30 where higher scores correspond to worse HRQoL.	1 week	[34]
	Skindex-29	29	1. Emotions 2. Functioning 3. Symptoms	Each question is scored from 0-5. Each domain is expressed on a 100-point scale. Higher scores indicate a lower level of HRQoL.	4 weeks	[137]
	Skindex-17	17	1. Symptoms 2. Psychosocial	Each question is scored from 0-3. The two domains have separate summing scores, ranging from 0–24 in the psychosocial and from 0–10 in the symptom subscale. Higher scores indicate a lower level of HRQoL.	4 weeks	[139]
	Skindex-16	16	1. Symptoms 2. Emotions 3. Functioning	Each question is scored from 0-6. Mean global index score, as well as each single domain are expressed on a 100-point scale. Higher scores indicate worse HRQoL.	4 weeks	[138]

HRQoL = health-related quality of life; MAU = multi-attribute utility measures

12.2 Appendix – Search terms used in the pemphigus systematic review

Patient population: pemphigus	#1	pemphigus(sh) OR pemphigus(ti,ab) OR bullous skin diseases(sh) OR ((autoimmune(ti,ab) OR skin(ti,ab)) AND (blistering(ti,ab) OR bullous(ti,ab) OR vesicobullous(ti,ab) OR vesicular(ti,ab)) AND (disease*(ti,ab) OR disorder*(ti,ab) OR dermatos?s(ti,ab)))
HRQoL related generic terms	#2	health status(sh) OR health stat*(tw) OR quality of life(sh) OR quality of life(tw) OR patient preference(sh) OR preference*(tw) OR utilit*(tw) OR questionnaire(sh) OR health survey(sh) OR self report(sh) OR well being(tw) OR wellbeing(tw) OR Quality-Adjusted Life Year(sh) OR QALY*(tw) OR Quality adjusted life year*(tw) OR Quality-adjusted life year*(tw) OR life quality(tw) OR QOL(tw) OR HRQL(tw) OR HRQoL(tw)
Instruments	#3	EuroQol(tw) OR EQ5D(tw) OR EQ-5D(tw) OR Health Utility Index(tw) OR Health Utilities Index(tw) OR HUI(tw) OR SF-6*(tw) OR SF 6*(tw) OR SF6*(tw) OR short form 6*(tw) OR shortform-6*(tw) OR short-form-6*(tw) OR shortform 6*(tw) OR SF-36(tw) OR SF36(tw) OR SF 36(tw) OR short form 36(tw) OR shortform 36(tw) OR shortform-36(tw) OR short-form-36(tw) OR RAND 36(tw) OR RAND-36(tw) OR RAND36(tw) OR SF-12(tw) OR SF12(tw) OR SF 12(tw) OR short form 12(tw) OR shortform 12(tw) OR shortform-12(tw) OR short-form-12 (sh,tw) OR Nottingham Health Profile(tw) OR NHP(tw) OR Quality of Wellbeing Index(tw) OR QWB(tw) OR Medical Outcomes Survey(tw) OR MOS(tw) OR Rosser(tw) OR WHOQOL-100(tw) OR WHOQOL 100(tw) OR World Health Organization Quality of Life assessment*(tw) OR WHOQOL-BREF(tw) OR WHOQOL BREF(tw) OR Assessment of Quality of Life(tw) OR AQoL(tw) OR DLQI(tw) OR Dermatology Life Quality Index(tw) OR Skindex*(tw)
Methods	#4	standard gamble(tw) OR time trade-off(tw) OR time trade off (tw) OR TTO(tw) OR Willingness to pay(tw) OR Willingness-to-pay(tw) OR WTP(tw)
All HRQoL studies	#5	#2 OR #3 OR #4
Animals	#6	animal(sh)
Humans	#7	#1 NOT #6
Publication type	#8	letter(pt) OR editorial(pt) OR conference abstract(pt)
All pemphigus HRQoL studies	#9	#5 AND #7 NOT #8

Search closed: 06/10/2014, Language limits: none

ab=abstract, pt=publication type, sh=subject heading, ti=title, tw=text word

Search strategy was based on the recommendations of Paisley et al. [169].

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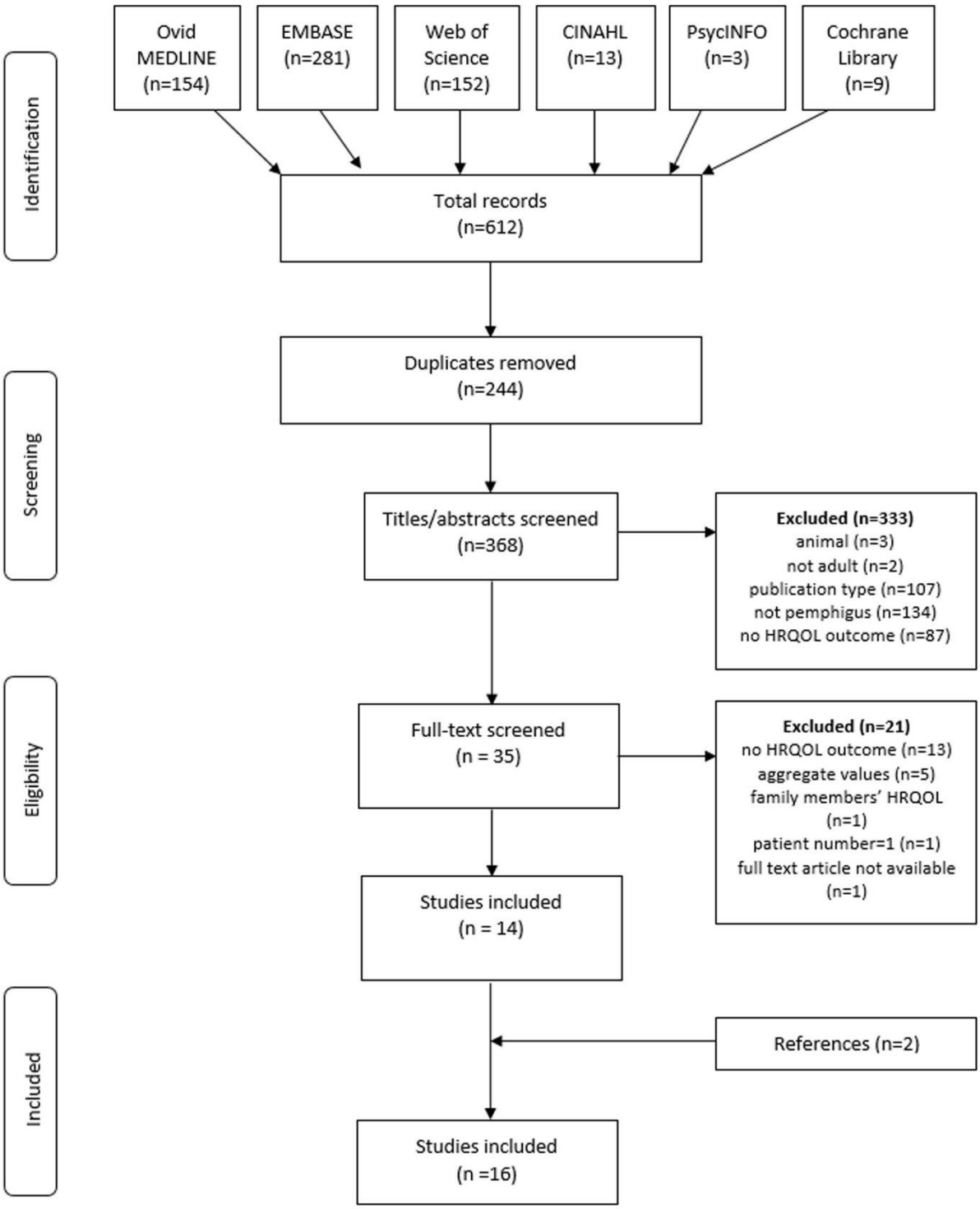
12.3 Appendix – PRISMA flowchart of the selection process



PRISMA flowchart: Moher et al. 2010 [182]

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12.4 Appendix – Inconsistencies in self-completed TTO answers

a) More than one indifference points with gaps between them

PEMPHIGUS		CANNOT DECIDE	PERFECT HEALTH	
10 YEARS		X		10 YEARS
10 YEARS	X			9.5 YEARS
10 YEARS		X		9 YEARS
10 YEARS			X	8 YEARS
10 YEARS	X			7 YEARS
10 YEARS		X		6 YEARS
10 YEARS			X	5 YEARS
10 YEARS		X		4 YEARS
10 YEARS	X			3 YEARS
10 YEARS	X			2 YEARS
10 YEARS			X	1 YEAR
10 YEARS		X		0 YEARS =IMMEDIATE DEATH

b) The point of indifference occurs after the respondent has stopped trading and refused further trading

PEMPHIGUS		CANNOT DECIDE	PERFECT HEALTH	
10 YEARS			X	10 YEARS
10 YEARS			X	9.5 YEARS
10 YEARS			X	9 YEARS
10 YEARS			X	8 YEARS
10 YEARS			X	7 YEARS
10 YEARS			X	6 YEARS
10 YEARS			X	5 YEARS
10 YEARS			X	4 YEARS
10 YEARS			X	3 YEARS
10 YEARS	X			2 YEARS
10 YEARS	X			1 YEAR
10 YEARS		X		0 YEARS =IMMEDIATE DEATH

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c) The point of indifference is followed by trading life years

PEMPHIGUS		CANNOT DECIDE	PERFECT HEALTH	
10 YEARS		X		10 YEARS
10 YEARS			X	9.5 YEARS
10 YEARS			X	9 YEARS
10 YEARS			X	8 YEARS
10 YEARS			X	7 YEARS
10 YEARS			X	6 YEARS
10 YEARS			X	5 YEARS
10 YEARS			X	4 YEARS
10 YEARS			X	3 YEARS
10 YEARS			X	2 YEARS
10 YEARS			X	1 YEAR
10 YEARS			X	0 YEARS =IMMEDIATE DEATH

12.5 Appendix – Tables and figures

Tables

Figures